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

Research Findings - Basic Research

Working Memory and the Endocannabinoid System

The endocannabinoid system has recently been proposed to modulate a variety of physiological processes, including those that underlie cognition. In the past year, NIDA researchers conducted studies to further elucidate the function of this system in learning and memory using mice lacking the endocannabinoid receptor (CB1). Findings from these studies showed that mice lacking the CB1 receptor exhibited significant deficits in a reversal task. Moreover, the deficit persisted despite being repeatedly shown the new task solution. These investigators also report that administration of three different cannabinoid agonists, delta-9-THC, WIN 55,212-2 and methanandamide disrupted performance in wild-type mice. Furthermore, these cannabinoid-agonist disruptive effects found in wild-type mice were blocked by the cannabinoid antagonist SR 141716A. These findings provide strong evidence that cannabinoids disrupt working memory through a CB1 receptor mechanism of action and suggest that the endocannabinoid system may have a role in facilitating extinction and/or forgetting processes. Varvel, S.A. and Lichtman, A.H. Evaluation of CB1 Receptors Knockout Mice in Morris Water Maze. Journal of Pharmacology and Experimental Therapeutics, 301(3), pp. 915-924, 2002.

Structural Adaptations in a Membrane Enzyme that Terminates Endocannabinoid Signaling

Endocannabinoids are naturally occurring compounds that bind to receptors in the brain and in peripheral tissues that are also the target of delta-9-tetrahydrocannabinol (THC), the active ingredient in marijuana. Researchers have been studying the brain's endocannabinoid system to learn more about its function. So far, endocannabinoids have been shown to modulate pain, cognition, feeding, and locomotor activity. In an article in the November 29, 2002, issue of Science, NIDA grantee, Dr. Benjamin Cravatt and his colleagues describe the crystal structure of an enzyme (FAAH) that terminates the activity of endocannabinoids. The structure of FAAH complexed with an arachidonyl inhibitor reveals how a set of discrete structural alterations allows this enzyme, in contrast to soluble hydrolases of the same family, to integrate into cell membranes and establish direct access to the bilayer from its active site. The intimate relationship between the active site of FAAH and cell membranes revealed by the enzyme's structure raises the possibility that fatty acid amides need not be transported through aqueous cellular compartments in order to proceed from site of action to site of degradation. As a consequence, proper endocannabinoid tone may rely on both the expression levels of FAAH and its localization relative to CB receptor systems in vivo. This knowledge should facilitate the design of novel targeted compounds that could be used to alter the activity of endocannabinoids, with the potential for use in treating pain, a variety of related nervous system disorders, and possibly marijuana addiction. Bracey, M.H., Hanson, M.A., Masuda, K.R., Stevens, R.C., and Cravatt, B.F. Structural Adaptations in a Membrane Enzyme that Terminates Endocannabinoid Signaling. Science, 298, pp. 1793-1796, 2002.

Bupropion and Nicotine-Like Discriminative Stimulus

Bupropion, an antidepressant approved in 1997 for smoking cessation, shares discriminative stimulus effects with cocaine and methamphetamine. The discriminative stimulus effects of these drugs, in turn, overlap with those of nicotine. Studies conducted by NIDA-supported researchers investigated the overlap in discriminative stimulus effects of bupropion and nicotine in a rodent model. These

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investigators found that bupropion substituted for nicotine. That is, the effects of bupropion were similar to nicotine using this procedure. However, bupropion effects were not blocked by a nicotine antagonist, mecamylamine, suggesting that bupropion may be producing its nicotine-like discriminative stimulus effects through neurobiological mechanisms different from nicotine itself. Given bupropion's shared pharmacology with dopamine transporter inhibitors and nicotine's effects on dopamine, these effects may be produced in part through bupropion's actions on dopaminergic neurotransmission. Wiley, J.E., LaVechia, K.L., Martin, B.R. and Damaj, M.I. Nicotine-like Discriminative Stimulus Effects of Bupropion in Rats. Experimental and Clinical Pharmacology, 10(2), pp. 129-135, 2002.

Opiate-Induced Analgesia and Role of Steroids

In a recent paper, Dr. Theodore Cicero and his associates at Washington University School of Medicine, St. Louis, determined the role of either the organizational or activational sex steroids in mediating gender differences observed in morphine-induced antinociception in the rat. To examine the organizational aspects, male pups were castrated early in life at postnatal days 1 and 2; females were masculinized by large doses of testosterone early in life on postnatal days 1 and 2. Older adult male and female rats were also castrated over a period of 2 months to examine the role of the acute activational effects of the opiates in the already sexually differentiated adult rat brain. The results showed that the gender differences in opiate analgesia were still evident in castrated older adult male and female rats. On the other hand, in male rats castrated early in life at postnatal days 1 and 2, the sensitivity to morphine analgesic effects was similar to females and, in fact, was almost identical to that observed in untreated females. Conversely, in female rats, masculinized by large doses of testosterone early in prenatal life, the morphine dose-response curve shifted to the left, yielding a dose-response curve similar to the dose-effect function seen in normal males. These results suggest that the sex differences that have been observed in morphine induced analgesia are due to the organizational effects of sex steroids in the early development of the rat brain, rather than to their acute activational effects occurring later in adulthood. These findings could be important in determining further gender differences and drug abuse liability. Cicero, T.J., Nock, B., O'Connor, L., and Meyer, E.R. Role of Steroids in Sex Differences in Morphine-induced Analgesia: Activational and Organizational Effects. Journal of Pharmacology and Experimental Therapeutics, 300, pp. 695-701, 2002.

Neuronal Nicotinic Receptor Ligands

There is interest in developing new nicotinic ligands in addition to those currently available, in part because of the diversity of nicotinic receptors in the brain. Nicotine receptors comprise various combinations of alpha and beta peptides, suggesting that ligands selective for these subtypes might have differing pharmacology. Additionally, there is an interest in attempting to separate the toxic side effects of nicotine or related nicotine compounds from their more positive potential medicinal uses in areas such as analgesia, depression, smoking cessation, and neuroimaging. Past efforts to modify the basic structure of nicotine have included the substitution of various groups on the pyridine ring (positions five and six), ring-opened analogs such as 3-aminomethyl or 3-aminoethylpyridines, or the introduction of other heterocyclic systems, such as the imidazole or isoxazole ring rather than the pyrrolidine ring of the parent nicotine. Drs. Linda Dwoskin and Peter Crooks have observed the structural similarity between d-tubocurarine (a dicationic competitive antagonist blocking cholinergic receptors) and bis dicationic nicotinic ligands separated by alkyl chains of varying length. This represents an extension of earlier work indicating that the addition of an alkyl group (such as octyl) to the pyridine nitrogen produced a nicotinic antagonist, capable of inhibiting nicotine binding (alpha4beta2) and blocking the nicotine-induced DA release from rat striatal slices. These researchers have now extended this work to the development of bis-azaaromatic quaternary ammonium analogues, in which two nicotine molecules (or two quinoline analogs) are present, positively charged on the pyridine nitrogen, and separated by an alkyl chain of varying length. The significant finding reported was that some of these structures exhibited considerable receptor selectivity for nicotine receptor subtypes. For example. a ten-carbon chain produced alpha4beta2 receptor antagonism alone in the bis-nicotine series, while a twelve-carbon chain in the bis-quinoline series produced alpha7 antagonism.. Ayers, J.T., Dwoskin, L.P., Deaciuc, A.G., Grinevich, V.P., Zhu, J., and Crooks, P.A. Bis-Azaaromatic Quarternary Ammonium Analogues: Ligands for alpha4beta2 and alpha7 Subtypes of Neuronal Nicotinic Receptors. Bioorganic & Medicinal Chemistry Letters, 12, pp. 3067-3071, 2002.

MDMA ("Ecstasy") Produces Severe Dopaminergic Neurotoxicity in Primates

After a Single Dose Regimen

The prevailing view is that MDMA is a selective serotonin neurotoxin, sparing noradrenergic terminals, and sparing dopaminergic terminals except at very high doses. Five squirrel monkeys were given 2 mg/kg subcutaneously 3 times, at 3-hour intervals, to model human MDMA use in a rave setting. Subjects received this regimen only once. One monkey was acutely symptomatic after two doses, and another died of hyperthermia. The other three, tested 2 weeks later, evidenced severe dopaminergic neurotoxicity and less serotonergic neurotoxicity. The investigators then repeated the experiment in 5 baboons (im route of administration). One died of hyperthermia, and one was acutely symptomatic. The neurotoxicity in the baboons was the same as in the monkeys. Noradrenergic axons and terminals were unaffected in both species. There was no evidence that MDMA induced parkinsonism, but the MDMA-treated monkeys were more sensitive to alpha-methyl-para-tyrosine (AMPT) -induced motor dysfunction. AMPT, a tyrosine hydroxylase inhibitor, gradually lowers dopamine levels. Earlier studies in primates generally involved administration of higher MDMA doses (5 or 10 mg/kg) twice daily, morning and evening, for 4 days, which engendered more severe toxicity toward brain serotonin neurons, with no long-term effects on brain dopamine neurons. One explanatory factor for dopaminergic neurotoxicity may be the result of closely spaced doses of MDMA resulting in a changed metabolic profile and nonlinear pharmacokinetics. Ricaurte, G.A., Yuan, J., Hatzidimitriou, G., Cord, B.J., and McCann, U.D. Severe Dopaminergic Neurotoxicity in Primates after a Common Recreational Dose Regimen of MDMA ("Ecstasy"). Science, 297(5590), pp. 2260-2263, 2002.

Methamphetamine-Induced Degeneration of Dopaminergic Neurons Involves Autophagy

Methamphetamine damages dopamine and serotonin-releasing neurons in primates and rodents when administered at levels equivalent to those abused by humans. The mechanism by which this drug induces neural damage, however, is not clear. An unusual aspect of the damage is that methamphetamine damages the axons and dendrites of neurons, but does not kill the neurons. The present work indicates that a novel cellular pathway, "neuronal macroautophagy," is responsible for this unusual form of degeneration. The authors showed that methamphetamine releases dopamine from synaptic vesicles, where it is normally stored and protected from breakdown, into the neuronal cytosol. Methamphetamine also increases dopamine synthesis. The excess dopamine in the cytosol oxidizes to produce highly reactive compounds that destroy cytosolic proteins by binding to the cysteine molecules that are common constituents of these proteins. This promotes the formation of "macroautophagic granules" in the dendrites and axons, which are visually striking, large, double layered organelles adapted for "swallowing" cellular constituents, and are mostly known for being induced in the liver during fasting or starvation. The granules, in an apparent attempt to save the neuron from death during periods of oxidative stress, consume the local axonal and dendritic consitutents and transport them to the cell body, thus destroying the neurites but saving the cell. Larsen, K. E., Fon, E.A., Hastings,T.G., Edwards, R.H., and Sulzer, D. Methamphetamine-induced Degeneration of Dopaminergic Neurons Involves Autophagy and Upregulation of Dopamine Synthesis. Journal of Neuroscience, 22(20), pp. 8951-60, 2002.

Pain Treatment Device Approved by FDA and is in Commercial Production

NIDA SBIR grantee Steven Michelson (Cyclotec Advanced Medical Technologies, Inc.) and his colleagues have developed and tested the CT1 pain control stimulator. The CT1 uses transcutaneous electrical nerve stimulation (TENS) technology, a technology that has been found over the past 30 years to be very effective in attenuating certain types of pain. The CT1 is a sophisticated yet simple device that delivers TENS directly to the areas in pain, without cumbersome wires or complicated electrode placements. This device has minimal side effects, and offers an effective alternative to drugs in the treatment of some types of pain. The device has recently received FDA approval as a pain treatment, and has gone into commercial production. A second generation TENS device (CT2) is now also being developed by Cyclotec with funding from a NIDA STTR grant.

Crystal Structures of Dipeptides Containing the Dmt-Tic Pharmacophore

Despite enormous progress in understanding the opioid systems of the brain, the mechanism of action of opioids is still not completely known. Neither the three-dimensional structures of the opioid receptors nor their ligand binding sites have been determined. There is need to design new opioid compounds to understand the opioid system as well as to provide leads for new therapeutic compounds that have fewer

side effects than the known existing compounds. An essential goal in the development of new opioid compounds is the formation of agonists and antagonists with a high degree of selectivity for either one specific opioid receptor subtype or a combination of characteristics that permit the ligand to interact with high affinity at two distinct receptors while eliciting opposite effects as a bi- or heterofunctional molecule. Toward this end, NIDA-supported investigators determined the crystal structures of three analogues of the potent delta-opioid receptor antagonist H-Dmt-Tic-OH (2',6'-dimethyl-L-tyrosine-L-1,2,3,4-tetrahydroisoquinoline-3-carboxylate), N,N(CH3)2-Dmt-Tic-OH (1), H-Dmt-Tic-NH-1-adamantane (2), and N,N (CH3)2-Dmt-Tic-NH-1-adamantane (3) were determined by X-ray single crystal analysis. Crystals of 1 were grown by slow evaporation, while those of 2 and 3 were grown by vapor diffusion. Compounds 1 and 3 crystallized in the monoclinic space group P2 1, and 2 crystallized in the tetragonal space group P43. Common backbone atom superimpositions of structures derived from x-ray diffraction studies resulted in root-mean-square (rms) deviations of 0.2-0.5 'A, while all atom superimpositions gave higher rms deviations from 0.8 to 1.2 'A. Intramolecular distances between the aromatic ring centers of Dmt and Tic were 5.1 'A in 1, 6.3 'A in 2, and 6.5 'A in 3. The orientation of the C-terminal substituent 1-adamantane in 2 and 3 was affected by differences in the psi torsion angles and strong hydrogen bonds with adjacent molecules. Despite the high delta-opioid receptor affinity exhibited by each analogue (ki < 0.3 nM), high mu-receptor affinity (ki < 1 nM) was manifested only with the bulky C-terminal 1-adamantane analogues 2 and 3. Furthermore, the bioactivity of both 2 and 3 exhibited mu-agonism, while 3 also had potent delta-antagonist activity. These data demonstrate that a C-terminal hydrophobic group is an important determinant for eliciting mu-agonism, whereas N-methylation maintained delta-antagonism. Furthermore, the structural results support the hypothesis that expanded dimensions between aromatic nuclei is important for acquiring mu-agonism. Bryant, S.D., George, C., Flippen-Anderson, J.L., Deschamps, J.R., Salvadori, S., Balboni, G., Guerrini, R., and Lazarus, L.H. Crystal Structures of Dipeptides Containing the Dmt-Tic Pharmacophore. Journal of Medicinal Chemistry, 45, pp. 5506-5513, 2002.

Increasing Brain Serotonin Activity Attenuates the Reinforcing and Neurochemical Effects of Cocaine in Monkeys

NIDA grantee Leonard Howell and his colleagues at the Yerkes Regional Primate Research Center in Georgia evaluated the ability of serotonergic (5-HT) treatments to modulate the reinforcing and neurochemical effects of cocaine in nonhuman primates. Alaproclate, a 5-HT uptake inhibitor, and quipazine, a 5-HT direct agonist, were examined first and found to decrease cocaine self-administration in a manner that was not due to nonspecific effects. The neurochemical bases of these effects were examined subsequently by means of in vivo microdialysis studies in awake monkeys. Pretreatment with either compound at doses that reduced self-administration of cocaine also attenuated cocaine induced elevation of brain dopamine. Although the interactions of the serotonergic and dopaminergic systems in manifestation of cocaine's behavioral and reinforcing effects are likely complex, these findings nonetheless suggest an important avenue for developing new medications to treat cocaine abuse. Czoty, P.W., Ginsberg, B.C., and Howell, L.L. Serotonergic Attenuation of the Reinforcing and Neurochemical Effects of Cocaine in Squirrel Monkeys. Journal of Pharmacology and Experimental Therapeutics, 300, pp. 831-837, 2002.

Chronic Morphine Exposure Induces a Spinal Dynorphin-Dependent Enhancement of Excitatory Transmitter Release From Primary Afferent Fibers

Paradoxical opioid-induced pain has been demonstrated repeatedly in humans and animals. The mechanisms of such pain are unknown but may relate to opioid-induced activation of descending pain facilitatory systems and enhanced expression and proprioceptive actions of spinal dynorphin. Dr. Frank Porreca and his research team at the University of Arizona tested the possibility that these opioid-induced central changes might mediate increased excitability to the spinal cord. Tactile and thermal hypersensitivity was observed at 7, but not 1, days after subcutaneous morphine pellet implantation; placebo pellets produced no effects. Basal and capsaicin-evoked release of calcitonin gene-related peptide (CGRP) was measured in spinal tissues taken from naive rats or rats on post-pellet days 1 and 7. The content and evoked release of CGRP were significantly increased in tissues from morphine-exposed rats at 7, but not 1, days after implantation. Morphine increased spinal dynorphin content on day 7 in rats with sham bilateral lesions of the dorsolateral funiculus (DLF) but not in rats with DLF lesions. Pharmacological application of dynorphin A(2-13), a non-opioid fragment, to tissues from naive rats enhanced the evoked release of CGRP. Enhanced evoked release of CGRP from morphine-pelleted rats was blocked by dynorphin antiserum or by previous lesions of the DLF. Sustained morphine induces plasticity in

both primary afferents and spinal cord, including increased CGRP and dynorphin content. Morphine-induced elevation of spinal dynorphin content depends on descending influences and enhances stimulated CGRP release. Enhanced transmitter release may allow increased stimulus-evoked spinal excitation, which is likely to be critical for opioid-induced paradoxical pain. Such pain may manifest behaviorally as antinociceptive tolerance. Gardell, L.R., Wang, R., Burgess, S.E., Ossipov, M.H., Vanderah, T.W., Malan, T.P., Jr., Lai, J., and Porreca, F. Sustained Morphine Exposure Induces a Spinal Dynorphin-dependent Enhancement of Excitatory Transmitter Release from Primary Afferent Fibers. Journal of Neuroscience, 22(15), pp. 6747-6755, 2002.

Neuronal Apoptosis Associated with Morphine Tolerance: Evidence for an Opioid-Induced Neurotoxic Mechanism

Tolerance to the analgesic effect of an opioid is a pharmacological phenomenon that occurs after its prolonged administration. Activation of the NMDA receptor (NMDAR) has been implicated in the cellular mechanisms of opioid tolerance. However, activation of NMDARs can lead to neurotoxicity under many circumstances. Dr. Mao at the Pain Center and his colleagues in the Neural Plasticity Research Group, at the Massachusetts General Hospital, Harvard Medical School, demonstrated that spinal neuronal apoptosis (cell death) occurred in rats made tolerant to morphine administered through intrathecal boluses or continuous infusion. The apoptotic cells were predominantly located in the superficial spinal cord dorsal horn, and most apoptotic cells also expressed glutamic acid decarboxylase, a key enzyme for the synthesis of the inhibitory neurotransmitter GABA. Consistently, increased nociceptive sensitivity to heat stimulation was observed in these same rats. Spinal glutamatergic activity modulated morphine-induced neuronal apoptosis, because pharmacological perturbation of the spinal glutamate transporter activity or coadministration of morphine with the NMDAR antagonist, (+)-5-methyl-10,11-dihydro-5H-dibenzo [a,d] cyclohepten-5,10-imine maleate, affected both morphine tolerance and neuronal apoptosis. At the intracellular level, prolonged morphine administration resulted in an upregulation of the proapoptotic caspase-3 and Bax proteins, and a downregulation of the anti-apoptotic Bcl-2 protein in the spinal cord dorsal horn. Furthermore, co-administration of morphine with N-benzyloxycarbonyl-Val-Ala-Asp-fluoromethyl ketone (a pan-caspase inhibitor) or acetyl-aspartyl-glutamyl-valyl-aspart-1-aldehyde (a relatively selective caspase-3 inhibitor) blocked morphine-induced neuronal apoptosis. Blockade of the spinal caspase-like activity also partially prevented morphine tolerance and the associated increase in nociceptive sensitivity. These results indicate an opioid-induced neurotoxic consequence regulated by the NMDAR-caspase pathway, a mechanism that may have clinical implications in opioid therapy and substance abuse. Mao, J., Sung, B., Ji, R-R. and Lim, L. Neuronal Apoptosis Associated with Morphine Tolerance: Evidence for an Opioid-Induced Neurotoxic Mechanism. Journal of Neuroscience, 22(17), pp. 7650-7661, 2002.

A Common Receptor and More Defined Pathway is Revealed for Stopping Neuronal Growth in its Tracks

Plasticity is the process by which the proper formation and breaking of connections among neurons occurs. Understanding neuronal plasticity is a goal for many behavioral neuroscientists because this process is fundamental to the acquisition of many types of memory and addiction. Plastic changes produced by drugs of abuse are likely to use the same mechanism as those employed during development and learning. A great deal of insight into the mechanism of plasticity has been obtained by studying the regulation of outgrowth and retraction of both axons (the cable-like structure that sends electrical impulses to end of the neuron) and dendrites (a cable-like structure involved in receiving and integrating the signals from neighboring neurons). Nogo-A, oligodendrocyte-myelin glycoprotein (OMgp), and myelin-associate glycoprotein (MAG) are three protein signals that are now known to inhibit neuronal outgrowth through a common pathway. Previous work has suggested that Nogo-A and MAG exert their actions through the Nogo receptor (NgR). In a 2002 Nature paper, Dr. Zhigang He and his colleagues demonstrate that OMgp also acts through the NgR. In a subsequent report in Nature, this same group showed that NgR elicits its inhibitory response indirectly, via the transmembrane protein p75. Since NgR is a GPI-linked receptor, it is not physically protruding into the cytoplasm. As a result, its connection to the cytoplasm had always been a mystery. Using either cultured cerebellar granule neurons or dorsal root ganglia neurons, the He group showed that p75 both physically interacts with NgR and was likely the transducer of the inhibitory signal. Both of these findings provide real insight into how axonal outgrowth is regulated. Given that this same NgR mechanism is used by neurons to direct plasticity in the regions of the brain associated with substance abuse (the cortex, amygdala and

others), this information should be very useful in our ability to understand, and potentially treat, addiction and other psychiatric disorders. In addition, this discovery has major implications for the development of small chemical ligands for the treatment of spinal cord injury. Wang, K.C., Koprivica, V., Kim, J.A., Sivasankaran, R., Guo, Y., Neve, R.L., and He, Z. Oligodendrocyte-myelin Glycoprotein is a Nogo Receptor Ligand that Inhibits Neurite Outgrowth. Nature, 417(6892), pp. 941-944, 2002; Wang, K.C., Kim, J.A., Sivasankaran, R., Segal, R., and He, Z. P75 Interacts with the Nogo Receptor as a Co-receptor for Nogo, MAG and OMgp. Nature, 420(6911), pp. 74-78, 2002.

Amphetamine Enhanced VTA Neuron Burst Firing and Phasic Release of DA May Account for Individuals' Tendency for Self-administration of Psychostimulants

Dr. John Williams and his colleagues found an adaptive change in the alpha-adrenergic receptors mediated membrane excitability of VTA dopamine neurons to psychostimulants. This was likely accompanied by a change in the pattern of dopamine release, which may account for individuals' tendency to self-administer psychostimulants. VTA dopamine neurons receive inputs from glutamatergic and noradrenergic neurons. Glutamatergic afferents activate both ionotropic and metabotropic glutamate receptors of the VTA dopamine neurons. Activation of the ionotropic glutamate receptor depolarized the DA neurons. Activation of the metabotropic glutamate receptors (mGlu) opens calcium-sensitive K+ channels and causes cell membrane hyperpolarization. The net result is a burst firing pattern of the DA neurons -- the ionotropic glutamate activation initiates neuron firing, which is followed by a transient pause due to the metabotropic glutamate hyperpolarization. The consequence is a phasic release of dopamine. The mGlu receptor-mediated hyperpolarization is attenuated and therefore the excitability of the VTA neuron is increased after activation of alpha adrenergic receptors, and dopamine receptors, similar to observations seen with the psychostimulants such as amphetamine or cocaine. The disinhibitory action of psychostimulants is mediated by the alpha-1 adrenergic receptor as their effects are reversed after application of the alpha-1 adrenergic receptor antagonist. The kinetics and attenuation of the magnitude of the membrane hyperpolarization would extend the depolarization of the DA neurons, curtail their burst activity and increase the phasic release of dopamine. The present results shed light on how the psychostimulant amphetamine acts at the cellular level. In addition, this research is implicating an alternative mechanism for how amphetamine might exert its effects on dopamine neurons and dopamine-dependent behavior. Paladini, C.A., Fiorillo, C.D., Morikawa, H., and Williams, J.T. Amphetamine Selectively Blocks Inhibitory Glutamate Transmission in Dopamine Neurons. Nature Neuroscience, 4(3), pp. 275-281, 2002.

Involvement of DARPP-32 Phosphorylation in the Stimulant Action of Caffeine

Dr. Lindskog and colleagues have elucidated some of the intracellular mechanisms that are involved in the stimulatory effects of caffeine on motor activity in mice. It had been previously reported by others that the psychostimulant effects of caffeine are due to blockade of adenosine A2A receptors. In the studies reported here, the investigators used A2A receptor agonist and antagonist reagents and mice lacking the DARPP-32 (dopamine- and cyclic AMP-regulated phosphoprotein of relative molecular mass 32,000) phosphoprotein to determine whether or not the motor activity of caffeine is regulated through DARPP-32. DARPP-32 is known for its role as a mediating molecule between slow and fast synaptic transmission. The activity of DARPP-32 is determined in part by the state of phosphorylation of various amino acids along the DARPP-32 molecule itself. What researchers found in this study is that caffeine, like adenosine A2A receptor antagonist, causes an increase in the phosphorylation of DARPP-32 at amino acid threonine 75. Phosphorylation at this particular residue makes DARPP-32 an inhibitor of a kinase known as PKA. These researchers expect that the caffeine-induced increase would lower PKA activity and provide a positive feedback amplification mechanism for shutting down adenosine A2A receptor-stimulated PKA signaling pathways. In this study they were able to demonstrate the involvement of DARPP-32 and its phosphorylation/dephosphorylation in the stimulant action of caffeine. Lindskog, M., Svenningsson, P., Pozzi, L., Kim, Y., Fienberg, A.A., Bibb, J.A., Fredholm, B.B., Nairn, A.C., Greengard, P., and Fisone, G. Involvement of DARPP-32 Phosphorylation in the Stimulant Action of Caffeine. Nature, 418(6899), pp. 774-778, 2002.

Elevated Expression of 5-HT1B Receptors in Nucleus Accumbens Efferents Sensitizes Animals to Cocaine

Although the effects of psychostimulants on brain dopamine systems are well recognized, the direct actions of cocaine on serotonin systems also appear to be important to its addictive properties. For example, serotonin actions at 5-HT1B receptors in the ventral tegmental area (VTA) modulate cocaine-induced dopamine release in the nucleus accumbens (NAcc) and alter the rewarding and stimulant properties of cocaine. However, the mechanisms of these effects have been unclear, because several neuron types in VTA express 5-HT1B receptors. One possibility is that 5-HT1B receptors on the terminals of GABAergic projections from NAcc to VTA inhibit local GABA release, thereby disinhibiting VTA neurons. Dr. Carlezon's lab tested this hypothesis directly by using viral-mediated gene transfer to overexpress 5-HT1B receptors in NAcc projections to VTA. A viral vector containing either epitope hemagglutinin-tagged 5-HT1B and green fluorescent protein (HA1B-GFP) cassettes or green fluorescent protein cassette alone (GFP-only) was injected into the NAcc shell, which sends projections to the VTA. HA1B-GFP injection induced elevated expression of 5-HT1B receptors in neuronal fibers in VTA and increased cocaine-induced locomotor hyperactivity without affecting baseline locomotion. Overexpression of 5-HT1B receptors also shifted the dose-response curve for cocaine-conditioned place preference to the left, indicating alterations in the rewarding effects of cocaine. Thus, increased expression of 5-HT1B receptors in NAcc efferents, probably in the terminals of medium spiny neurons projecting to the VTA, may contribute to psychomotor sensitization and offer an important target for regulating the addictive effects of cocaine. Neumaier, J.F., Vincow, E.S., Arvanitogiannis, A., Wise, R.A., and Carlezon, W.A., Jr. Elevated Expression of 5-HT1B Receptors in Nucleus Accumbens Efferents Sensitizes Animals to Cocaine. Journal of Neuroscience, 22, pp. 10856-10863, 2002.

Extinction-Induced Upregulation in AMPA Receptors Reduces Cocaine-Seeking Behavior

Preventing relapse is the greatest challenge to successful treatment of drug addiction. Furthermore, the risk of relapse may be present at almost anytime during the period of abstinence, from a few days to a few years, and is especially pronounced during stressful situations. Relapse may be reduced, however, through extinction training, a procedure wherein drug-seeking behavior is no longer reinforced by drug administration. In a recent report, Dr. David Self and his colleagues demonstrate that extinction training during withdrawal from cocaine self-administration in rats produces increases in GluR1 and GluR2/3 subunits of AMPA glutamate receptors in the shell of the nucleus accumbens (NAcc), a brain region critical for cocaine reward. Following the acquisition of cocaine self-administration, three groups of rats were withdrawn from cocaine for one week under different conditions. The extinction group (EXT) was returned to the self-administration environment, but lever presses no longer delivered cocaine; the home cage group (HC) remained undisturbed in the home cage during this time; the levers retracted group (LR) was returned to the self-administration environment, but the levers were unavailable. Thus, only Group EXT had the opportunity to learn the futility of lever responding and, as expected, this group ceased responding compared to the HC and LR groups. The new finding is that extinction training increased the amount of GluR1 and GluR2/3 subunits in the NAcc shell and the GluR1 increase was directly related to the level of extinction achieved, suggesting that GluR1 might promote extinction of cocaine seeking. Dr. Self and his colleagues confirmed this hypothesis by demonstrating that viral-mediated over-expression of these receptor subunits in the NAcc facilitated cocaine-seeking but not sucrose-seeking responses. Moreover, another experiment demonstrated that the facilitatory effect of GluR on extinction is due to reduced motivation to seek cocaine, not to the enhancement of extinction learning. A final experiment demonstrated that a single extinction session, when conducted during GluR over-expression, attenuated stress-induced (but not cue- or drug prime-induced) relapse to cocaine seeking behavior, even after GluR levels returned to baseline levels. In summary, these results indicate that extinction-induced changes in glutamate receptors may facilitate control over cocaine seeking by restoring glutamatergic tone in the NAcc, and, thereby, reduce the propensity for relapse under stressful conditions after prolonged abstinence. The results also suggest that behavioral approaches have the potential to reverse or ameliorate the harmful consequences of drug use. Sutton, M.A., Schmidt, E.F., Choi, K.H., Schad, C.A., Whisler, L., Simmons, D., Karanian, D.A., Monteggia, L.M., Neve, R.L., and Self, D.S. Extinction-induced Upregulation in AMPA Receptors Reduces Cocaine-seeking Behaviour. Nature, 421, pp. 70-75, 2002.

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Research Findings - Behavioral Research

Sex Differences in Running-Wheel Attenuation of Cocaine Self-administration in Rats

Previous animal studies have shown that the acquisition of drug self-administration can be reduced by the availability of alternative drug or nondrug reinforcers. Other studies have shown that exercise via wheel running can reduce established oral amphetamine and oral ethanol self-administration. Dr. Marilyn Carroll and her colleagues at the University of Minnesota have now reported that wheel running can also reduce established i.v. cocaine self-administration. The effect, however, occurred in females, but not males. After a baseline of wheel running was established, access to the wheel was terminated and rats were trained to self-administer cocaine (0.2mg/kg). Next, rats were given concurrent access to both cocaine self-administration and the running wheel, followed by a period of access only to cocaine and then a period of wheel only. The researchers found that providing concurrent access to both the wheel and cocaine produced: (A) a suppression of cocaine self-administration (relative to the cocaine-only period) that was significant in females (70.6%), but not in males (21.9%) and (B) a suppression in wheel running revolutions (relative to the wheel-alone period) in both males (63.7%) and females (61.5%). These data indicate that for females, but not males, wheel running can serve as an alternative reinforcer that significantly competes with established cocaine self-administration and that cocaine and wheel running are substitutable reinforcers. These data, along with research with humans indicating that exercise is an aid in human smoking cessation, suggest that exercise may be a useful adjunct in the treatment of cocaine dependence, especially for women. Cosgrove, K.P., Hunter, R.G. and Carroll, M.E. Wheel-Running Attenuates Cocaine Self-administration in Rats - Sex Differences. Pharmacology, Biochemistry and Behavior, 73, pp. 663-671, 2002.

Estrogen Plays a Role in the Acquisition of I.V. Heroin Self-Administration in Female Rats

Prior research from the laboratory of Dr. Marilyn Carroll of the University of Minnesota has shown that female rats acquire i.v. self-administration of both cocaine and heroin faster than male rats. Subsequent work from that laboratory found that blocking of estrogen, either surgically or chemically, reduced the percentage of females that met the acquisition criterion for cocaine self- administration. In the present experiment, Dr. Carroll and her colleagues assessed whether estrogen plays a similar role in heroin self-administration. Acquisition of low-dose (0.0075 mg/kg) heroin self-administration was examined in two estrogen groups, (a) ovariectomized (OVX) females treated with estradiol benzoate (OVX-EB) and (b) sham-operated (SH) females treated with the vehicle (SH-VEH). In a third group, estrogen was surgically blocked via ovariectomy and the females were treated with vehicle (OVX-VEH). The researchers report that the OVX-EB rats met criterion in significantly fewer days than the OVX-VEH (6.4 vs. 12.9) and self-administered more heroin infusions than the OVX-VEH rats. Unexpectedly, the SH-VEH group failed to exhibit faster acquistion than the OVX-VEH group, an outcome for which the researchers discuss several possible explanations. These data join a growing body of literature (from studies both in human subjects and preclinical research) demonstrating that estrogen influences the vulnerability to develop drug abuse behaviors and emphasizes the need for further research aimed at uncovering mechanisms for this effect. Roth, M.E., Casimir, A.G. and Carroll, M.E. Influence of Estrogen in the Acquisition of Intravenously Self-administered Heroin in Female Rats. Pharmacology, Biochemistry and Behavior, 72, pp. 313-318, 2002.

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Early Life Stress in an Animal Model Accelerates Tolerance and Sensitization

A common procedure for inducing early life stress is maternal separation (MS), wherein rat pups are removed from the dam for several hours each day. Maternal separation produces profound changes in the brain's endogenous stress system and alters an animal's ability to respond to stress during adulthood. Concomitant with these changes in stress reactivity, animals are more responsive to behavioral effects of psychostimulants and more readily acquire drug self-administration. Dr. Stephen Holtzman and colleagues have reported that tolerance to the analgesic effects of morphine is also altered by early MS, and in a recent study, his research group found evidence that early life stress affects neuroadaptations that give rise to the behavioral effects of repeated morphine. These studies examined the effects of daily MS upon reactivity to a novel environment and to morphine-induced sensitization and tolerance when animals were tested as adults (more than 90 days old). MS litters were removed for 3 hrs daily on neonatal days 2-14. Handled (H) control pups were treated similarly but removed for only 15 min daily, and non-handled (NH) controls were left undisturbed with the dam until weaning. Results indicated that MS had a significant effect on the offspring's reactivity to a novel environment and to the development of opiate tolerance and sensitization as measured by changes in locomotor activity. Thus, MS rats exhibited robust increases (50-75%) in locomotor activity in a novel environment compared to NH controls; whereas H rats showed only modest increases (30%). When treated with 10mg/kg morphine repeatedly, only MS and H rats showed suppression of activity (horizontal counts) after the first and second injection. Tolerance to this initial behavioral suppression was observed over 10 drug administrations so that at the end of the 10 day treatment regimen, drug-induced activity seen in MS rats was double that of the NH controls, suggesting a sensitization of opiate-induced behavioral stimulation. Next, animals were withdrawn for 2 days and challenged with saline in an environment that had been paired with morphine. On this test for conditioned sensitization, only MS rats showed locomotor stimulation, suggesting that these animals had become conditioned to the drug paired environment. This observation is intriguing, in light of previous findings to suggest that repeated early MS is associated with enhanced long-term potentiation (LTP) -- a neural mechanism that may subserve associative processes of conditioning. The authors suggest that MS animals show an enhanced sensitivity to opiate-induced neuroadaptive phenomena, brought about by early life stress. Moreover, the acceleration of these neuroadpative processes may be linked to early developmental alterations in opioid receptor systems. Kalinichev, M., Easterling, K.W. and Holtzman, S.G. Early Neonatal Experience of Long-Evans Rats Results in Long-lasting Changes in Reactivity to a Novel Environment and Morphine-induced Sensitization and Tolerance. Neuropsychopharmacology, 27, pp. 518-533, 2002.

Adolescent Rats Respond Differently to Repeated Cocaine than Adults

Behavioral and neurochemical models of drug reactivity during the adolescent period are useful for studying influences on the vulnerability to acquire drug abuse behaviors or escalation to drug addiction during the teen years. Dr. Sari Izenwasser and colleagues have recently compared adult (170-200 g body weight) and periadolescent rats (75-100 g body weight) with behavioral and receptor-binding measures during repeated treatments with cocaine. Rats in these studies were given 50 mg/kg cocaine daily (in two injections) for 7 days. On day 8 and 16, a probe was conducted to determine if conditioned sensitization of locomotor activity was induced in the cocaine-paired environment. Then, on day 17, all animals were challenged with 15 mg/kg cocaine, and locomotor behavior and stereotypy were measured. In separate groups of animals, quantitative autoradiography was performed on post-mortem samples to measure D1 and D2 dopamine receptors, along with dopamine (DAT) and serotonin (SERT) transporter density. Cocaine increased behavioral activity over all seven days, in both adult and adolescent rats. However, whereas adult animals showed a sensitization Ð i.e., increased locomotor activity over the 7 days, adolescent rats had an enhanced level of responding that remained constant, suggesting that they did not develop the behavioral sensitization seen in adults. Stereotypy was constant over all 7 days for both groups, indicating that this difference cannot be attributed to changes in stereotypical behaviors. None of the animals showed a conditioned behavioral response when injected with saline on days 8 or 16. However, upon challenge with 15 mg/kg cocaine after the chronic treatment regimen, only the adult rats with chronic cocaine experience showed a sensitized locomotor response (i.e., greater than the adult rats treated for 7 days with saline). By contrast, periadolescent rats treated with 7 days of 50mg/kg cocaine or the vehicle had a very similar level of behavioral stimulation to the test dose of cocaine. This observation further demonstrates that periadolescent rats did not develop behavioral sensitization, whereas the adults clearly did. Neurochemical findings parallel these behavioral data,

in that adult animals had an increase in DAT density in caudate putamen areas, whereas periadolescent animals showed no change from controls. Furthermore, while D1 and D2 receptors were unchanged in both groups, SERT densities were increased in several areas measured from adults, but not periadolescents. Collectively these observations suggest that adolescent rats are less sensitive to neuroadaptations induced by repeated psychostimulant treatment than are adults. The authors suggest that perhaps a neurobiological developmental process may counteract the development or expression of these drug-induced neuroadaptive changes. Collins, S.L. and Izenwasser, S. Cocaine Differentially Alters Behavior and Neurochemistry in Periadolescent Versus Adult Rats. Developmental Brain Res., 138, pp. 27-34, 2002.

Devaluation of Natural Rewards: Cocaine-Induced Suppression of Saccharin Intake

It is commonplace to observe that drug addicted individuals choose drugs when given a choice between drugs and natural rewards (food, sex, recreation, etc.). Why this occurs is not fully understood, but according to Dr. Patricia Grigson's "Reward Comparison" hypothesis, natural rewards are devalued when they occur in association with more salient drug rewards. That is, in Dr. Grigson's research, rats learn to devalue a natural reward like saccharin, as a result of paired presentations of saccharin with more salient natural (e.g., sucrose) or drug rewards (e.g., morphine). In the present research, thirsty rats were given 5 min access to saccharin followed by the opportunity to self-administer cocaine (or saline). Results indicated that rats avoided intake of saccharin after saccharin-cocaine pairings and that greater avoidance of saccharin was associated with higher (subsequent) rates of cocaine self-administration. When evaluated in terms of individual differences in saccharin intake, the data revealed two separate patterns, or associations between saccharin avoidance and cocaine self-administration: A group of 'small suppressers' that consumed the natural saccharin reward but subsequently took few drug infusions; and a second group of 'large suppressers' that avoided intake of saccharin but initiated three times as many infusions of cocaine. Moreover, avoidance of the saccharin cue and the propensity to self-administer cocaine were both maintained after at least one month of abstinence, as were the individual patterns described above. The neurobiological substrates for these effects are not yet known, but the gustatory thalamus and the mesolimbic dopamine pathway have been implicated. Finally, although the tendency to compare rewards can lead to the devaluation of a natural reward, evidence suggests that under the right circumstances, a highly reinforcing natural reward can lead to the devaluation of a drug of abuse. The treatment implications of this particular circumstance demand further attention. Grigson, P.S., and Twining, R.C. Cocaine Induced Suppression of Saccharin Intake: A Model of Drug-induced Devaluation of Natural Rewards. Behavioral Neuroscience, 116(2), pp. 321-333, 2002.

Discounting Future Events and Drug Addiction

Investigators at the University of Vermont have shown that substance use disorder is associated with excessive temporal discounting of delayed rewards. Their research has clearly shown that individuals addicted to drugs of abuse such as heroin and nicotine (tobacco) value future events less than non-addicted individuals. Little is known, however, about whether or not an individual's temporal discounting changes with the "drug state" (i.e., having just used the drug vs. not having used for a period of time). To examine how drug state affects an individual's discount rate, opioid-dependent subjects maintained on buprenorphine completed a hypothetical choice task in which they chose between an immediate smaller outcome or a larger more delayed outcome. Results showed that an individual's preference for the immediate smaller reward was greater just before they received buprenorphine, when they were in a relatively less medicated state, than following buprenorphine administration. These results have important clinical implications. First, the "myopic" temporal horizon observed in these individuals, regardless of medicated state, suggests that immediate and rewarding outcomes are needed in drug treatment settings, such as are used in contingency management therapies or 12-step approaches. Furthermore, clinical research will be able to capitalize on this discovery to develop more effective treatment interventions. Finally, these findings suggest that drug withdrawal or being in a less medicated state is associated with more impulsivity which may subsequently lead to high risk patterns of behavior. Giordano, L.A., Bickel, W.K., Loewenstein, G., Jacobs, E.A., Marsch, L., and Badger, G.J. Mild Opioid Deprivation Increases the Degree that Opioid-dependent Outpatients Discount Delayed Heroin and Money. Psychopharmacology, 163, pp. 174-182, 2002.

Differential Drug Access Determines the Pattern of Cocaine Self-

administration and Influences Reinforcing Efficacy

Humans usually begin to use cocaine on an occasional or limited daily basis, and then, although patterns vary between individuals, most addicts progress to binging and compulsive use. Dr. David Roberts and his colleagues have been developing procedures for cocaine self-administration in rats that closely model the development of human usage patterns. In a recent investigation (Roberts et al., 2002) using their discrete trials (DT) procedure, rats were allowed to press a lever to receive cocaine 24 hrs a day, but different groups of animals were limited to either 2, 3, 4, or 5 discrete trials per hour (dosage of 1.5 mg/kg/injection) for 21 days. Both the circadian pattern and the total amount of cocaine intake were correlated with the number of discrete trials allowed. For example, animals on the DT2 schedule (two trials per hour) took 80% of their injections in the dark phase of the light:dark cycle, whereas animals on the DT5 schedule self-administered almost round the clock, with only 60% of their injections in the dark phase. Average total intake for the DT2 group was about 20 mg/kg/day, whereas the DT5 group self-administered an average of almost 100 mg/kg/day. Remarkably, this procedure allows for very high cocaine intake without toxicity. Animals in the DT3, 4 and 5 groups also showed binge-like behavior over the first 2-3 days, but responding stabilized thereafter. At the end of the 21 days, the DT5 animals were tested using a progressive ratio (PR) schedule to determine whether they found cocaine more or less reinforcing compared to a PR pretest, given before the discrete trials schedule began. At all doses tested (0.38, 1.5 and 3.0 mg/kg/inj), breakpoints in the post-test were lower than in the pretest, indicating that animals had developed tolerance to the reinforcing effects of cocaine from their very high intake during the DT schedule. In a separate set of experiments (Morgan et al., 2002), the DT procedure was used to investigate whether a history of different patterns of drug intake would increase the reinforcing efficacy of cocaine after various periods of abstinence. With the PR test, animals exposed to DT4 conditions for either 7 or 10 days showed a slight (but not significant) decrease in breakpoint when retested immediately, or with one day of abstinence, after the DT schedule ended. However, breakpoints significantly increased after 7 days of abstinence. This finding is in agreement with animal studies and clinical impressions indicating that there is an "incubation" of drug-seeking behavior that develops over the withdrawal period. The current study is the first to demonstrate that the reinforcing efficacy of cocaine increases over time "off drug". Roberts, D.C.S., Brebner, K., Vincler, M., and Lynch, W.J. Patterns of Cocaine Self-administration in Rats Produced by Various Access Conditions Under a Discrete Trials Procedure. Drug and Alcohol Dependence 67, pp. 291-299, 2002; Morgan, D., Brebner, K., Lynch, W.J., and Roberts, D.C.S. Increases in the Reinforcing Efficacy of Cocaine after Particular Histories of Reinforcement. Behavioural Pharmacology, 13, pp. 389-396, 2002.

Tolerance to the Disruptive Effects of Marijuana on Learning in Rats

Considering the widespread use of marijuana by school age adolescents and young adults, determination of marijuana's acute and chronic effects on learning is critically important. Chronic administration of marijuana is known to produce both tolerance and dependence (i.e., a withdrawal syndrome). The present study investigated the effects of tolerance and dependence following chronic administration of delta-9-THC (THC), the psychoactive ingredient in marijuana, on learning and performance in rats. Animals were trained on a complex discrimination to make sequences of three responses for food reinforcement. The discrimination was arranged such that drug effects could be evaluated separately on the learning (i.e., acquiring a new response sequence) and on the performance (i.e., executing a learned sequence) components of the task. The acute and chronic effects of THC were examined. To study the effects of dependence induced by repeated THC administration, learning and performance were also assessed after administration of a cannabinoid (CB1) receptor antagonist in chronically treated animals. Results indicated that a 5.6 mg/kg dose of THC disrupted learning and performance of the discrimination, but that tolerance developed to both the rate-decreasing and error-increasing effects of this dose during the learning and the performance components of the task. During chronic administration of THC, the CB1 antagonist, SR141716A, was occasionally given in place of THC. Whereas 1 mg/kg SR141716A alone is without effect on learning and performance measures in this paradigm, when substituted for THC in monkeys receiving a repeated regiment of THC injections, it selectively increased errors in learning but had little or no effect on performance. These data demonstrate that learning is more sensitive than performance to the disruptive effects of chronic dosing with THC, and suggest that this paradigm is useful for detecting subtle disruptions in cognitive function under conditions of withdrawal from THC. Delatte, M.S., Winsauer, P.J., and Moerschbaecher, J.M. Tolerance to the Disruptive Effects of delta-9-THC on Learning in Rats. Pharmacology, Biochemistry & Behavior, 74(1), pp. 129-140, 2002.

The Cocaine Metabolite, Cocaethylene, May Prolong Euphoria and Attenuate Cocaine's Anxiogenic Effects

Dr. Aaron Ettenberg and his colleagues at the University of California have previously demonstrated that cocaine has both rewarding and anxiogenic effects. In their behavioral procedure, rats are trained to run a straight alley to receive a single cocaine injection. Animals show a pattern of "approach-avoidance" responding in this alley, suggesting that they retain a mixed association of both reward and anxiety with the drug-associated environment, prompting occasional 'retreats' during their traverse down the alley to the goal box. In a new study, the investigator was interested in the effects of concurrent alcohol on this biphasic effect of cocaine. Clinical studies report that alcohol prolongs the cocaine "high" while reducing any associated anxiety. Dr. Ettenberg proposed that the ethyl ester of the cocaine metabolite benzoylecgonine -- cocaethylene (CE) -- might be responsible for this effect. CE is formed only when alcohol is present with cocaine in the liver and has been observed to have many of the same behavioral effects of cocaine, suggesting that CE induces psychostimulant-like euphoria. However, CE has a more delayed onset of action than cocaine, so although it also produces a later anxiogenic effect, a prolongation of the positive/pleasant effects from CE may mask the aversive effect of cocaine. To test his hypothesis, the investigator administered i.v. cocaine or CE and tested animals in a conditioned place preference (CPP) procedure at various times after drug or metabolite infusion. Cocaine produced the usual place preference when conditioning (placement into the box) took place immediately after cocaine infusion, but animals that were not placed into the apparatus until 15 min after cocaine showed an aversion to the drug-paired environment during testing. Rats given i.v. CE were conditioned to the CPP apparatus at 0 min, 5 min, 15 min, and 30 min following CE infusion. As expected, a place preference developed in CE rats placed immediately into the box, but an aversion was seen in rats that had been exposed to the box 30-min post-administration. The aversion seen 30 min post-CE, however, was not as strong as that seen after 15 min post-cocaine. Thus, the time course of CE-induced reward and aversion appear consistent with the metabolite's relatively long half-life. Accordingly, the delayed euphoria induced by CE may indeed mask a dysphoric effect of cocaine when co-administered with alcohol, because plasma CE levels remain high even as an aversive opponent process is induced by falling cocaine plasma concentrations. Knackstedt, L.A., Samimi, M.M. and Ettenberg, A. Evidence for Opponent-process Actions of Intravenous Cocaine and Cocaethylene. Pharmacology, Biochemistry and Behavior, 72, pp. 931-936, 2002.

Only Five Days of Cocaine Self-administration Activates Brain Circuits Involved in Working Memory

Dr. Linda Porrino and her colleagues have been using a metabolic mapping technique (the 2-[14C]deoxyglucose method) to define brain circuits that are activated during various stages of cocaine dependency. The purpose of the current study was to define substrates that mediate the initial effects of cocaine in a nonhuman primate model of cocaine self-administration. While most brain imaging studies with human subjects are typically carried out on subjects who are already dependent, this primate model is ideally suited for identifying neurobiological correlates of drug-seeking and drug-taking behavior in the early stages of substance dependence. Rhesus monkeys were trained to self-administer cocaine and compared with monkeys trained to respond under an identical schedule of food reinforcement, over a five-day period, to model initial stages of drug taking in humans. Cocaine self-administration reduced glucose utilization in the mesolimbic system, including the ventral tegmental area, ventral striatum, and medial prefrontal cortex Ð paralleling areas previously identified as being activated by experimenter-administered cocaine. However, in the current study, following self-administration, metabolic activity was also found to be increased in the dorsolateral and dorsomedial prefrontal cortex, and in the mediodorsal nucleus of the thalamus Ð areas not activated by non-contingent drug delivery in the previous study. These findings reveal that self-administered cocaine engages additional brain circuits not activated merely by the pharmacological actions of this drug. Because these additional brain areas are involved in working memory, the present findings suggest that strong associations between cocaine and the internal and external environment are formed from the very outset of cocaine self-administration. Porrino, L.J., Lyons, D., Miller, M.D., Smith, H.R., Friedman, D.P., Daunais, J.B. and Nader, M.A. Metabolic Mapping of the Effects of Cocaine during the Initial Phases of Self-administration in the Nonhuman Primate. Journal of Neuroscience 22, pp. 7687-7694, 2002.

Tracking the Conditioned Effects of Cocaine During Abstinence

Human addicts are known to have persistent changes in indices of brain chemistry for

a prolonged period of time after drug use has subsided. Likewise, cravings for cocaine are reported to be long-lived and persistent, providing the greatest challenge to effective treatment. Animal models have recently been extending the imposed withdrawal period and examining changes in underlying neurobiological substrates that may be associated with continued drug-seeking and craving or relapse. For example, exposure to drug-associated cues can prompt drug-seeking in rats previously self-administering cocaine for up to 4 months after extinction. Recent studies in the laboratory of Dr. Conan Kornetsky have mapped changes in brain glucose utilization (using 2-deoxy-D-[l-14C]glucose, or 2-DG) at 6 and 13 days after only a few high doses of morphine. They have found that changes are more widespread when animals have been conditioned to a morphine-paired environment and glucose utilization is assessed after placement back into this environment. Thus, with this technique, the investigators are able to ascertain which areas and circuits are activated by conditioned associations, long after an animal has received the drug. In the study reported here, rats were treated with 30mg/kg of cocaine or the saline vehicle, once daily for 7 consecutive days. Half of the rats were treated in the 2-DG chamber, where they remained for 1 hour following drug or saline administration, and others received injections in the home cage. On the eighth day after daily injections were stopped, all rats were sacrificed after 45 minutes in the 2-DG environment. The investigators noted a more extensive pattern of changes in glucose utilization in cocaine-conditioned animals (cocaine paired with 2-DG environment), than in those from the unconditioned group (cocaine paired with home cage). Local cerebral metabolic rates of glucose (LCMRglu) were significantly different from control rats in 12 areas from the conditioned group, and in only four from the unconditioned group. Common areas of decreased LCMRglu included the ventrolateral orbital cortex, the anterior nucleus accumbens, and area CA3 of the hippocampus -- indicating persistent changes in activity of these regions eight days after cessation of drug. But in addition, conditioned animals had decreased LCMRglu in the agranular insular cortex, the dorsomedial and lateral caudate, the basolateral amygdaloid nucleus, the subiculum, the medial and lateral thalamus and the lateral habenular nucleus. This differential pattern of activation implicates these additional structures in the long-lasting associations that form between cocaine and its associated environment. Involvement of structures such as the basolateral amygdala and the ventral subiculum have in fact been implicated in relapse, from studies of reinstated cocaine-seeking behavior in animals previously extinguished from self-administration. Future studies employing this 2-DG methodology hold potential to examine patterns of activation in animals withdrawn from drug, (including self-administered drug), over a more protracted period of time and thus, continue to map out the potential circuits of prolonged drug craving. Knapp, C.M., Printseva, B., Cottam, N. and Kornetsky, C. Effects of Cue Exposure on Brain Utilization 8 Days after Repeated Cocaine Administration. Brain Research, 950, pp. 119-126, 2002.

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

Research Findings - Treatment Research and Development

Brain Reward System Activity In Major Depression and Comorbid Nicotine Dependence

Busto and colleagues at the Center for Addiction and Mental Health, University of Toronto, studied the response to oral d-amphetamine as a probe for the functioning of the brain reward system in nicotine-dependent, non-medicated subjects with a diagnosis of major depressive disorder (MDD) and 16 nicotine-dependent, control subjects. Smoking did not modify the response to d-amphetamine in MDD or control subjects, but decreased overall negative mood state during placebo sessions. A significant correlation between depression severity (Hamilton depression scale) and d-amphetamine rewarding effects was found in MDD smoker subjects. Severity of depression was significantly correlated with increased rewarding effects of d-amphetamine. Thus, chronic nicotine use does not modify response to d-amphetamine even though the brain reward system may be dysfunctional in subjects with major depression. Cardenas, et al., J. Pharmacol. Exp. Ther., 302, pp. 1265-1271, 2002.

Activation in Medial Temporal Lobe and Visuospatial Neural Circuits Elicited by Smoking Cues

Huettel and colleagues at Duke University used BOLD fMRI to investigate the neural substrates modulated by visual smoking cues in nicotine-deprived smokers and a nonsmoking comparison group. Subjects viewed a pseudo-random sequence of smoking images, neutral nonsmoking images, and rare targets (photographs of animals). Subjects pressed a button whenever a rare target appeared. In smokers, the fMRI signal was greater after exposure to smoking-related images than after exposure to neutral images in medial temporal lobe circuits activated by addictive drugs (right posterior amygdala, posterior hippocampus, ventral tegmental area, and medial thalamus) as well visuospatial attention regions (bilateral prefrontal and parietal cortex and right fusiform gyrus). None of these areas was activated in nonsmokers by the smoking images. In nicotine-deprived smokers, smoking cues are processed like rare targets in that they activate attentional regions as well as medial temporal lobe regions. Due et al., Am. J. Psychiatry, 159, pp. 954-960, 2002.

Dissociable Prefrontal Brain Systems for Attention and Emotion

LaBar and colleagues at Duke University used fMRI to determine whether attentional and emotional functions are segregated into dissociable prefrontal networks in the human brain. Normal subjects discriminated infrequent and irregularly presented attentional targets (circles) from frequent standards (squares) while novel distracting scenes, parametrically varied for emotional arousal, were intermittently presented. Targets differentially activated middle frontal gyrus, posterior parietal cortex, and posterior cingulate gyrus. Novel distracters activated inferior frontal gyrus, amygdala, and fusiform gyrus, with significantly stronger activation evoked by the emotional scenes. The anterior cingulate gyrus was the only brain region with equivalent responses to attentional and emotional stimuli. These results show that attentional and emotional functions are segregated into parallel dorsal and ventral streams that extend into prefrontal cortex and are integrated in the anterior cingulate. Yamasaki et al., Proc. Natl. Acad. Sci., 99, pp. 11447-11451, 2002.

Relationships among BOLD, CBV, and CBF Changes in Rat Brain

Li and colleagues at the Medical College of Wisconsin used fMRI to compare arterial cerebral blood flow (CBF (A)) and total cerebral blood volume (CBV (T)) in rats.

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Urethane-anesthetized rats were examined under graded hypercapnia conditions (7.5% and 10% CO (2) ventilation) for changes in blood oxygenation level-dependent (BOLD) contrast and and CBV (T) using a monocrystalline iron oxide nanocolloid (MION) contrast agent. It was found that the relationship between CBV (T) and CBF (A) under transient conditions is similar to the power law under steady-state conditions. In addition, the transient relationship between CBV (T) and CBF (A) was region-specific. Voxels with large (<15%) BOLD signal changes from hypercapnia (7.5% CO(2) ventilation) had a larger power index (alpha = 3.26), a larger maximum possible BOLD response, and shorter T(*) (2) caused by deoxyhemoglobin, compared to voxels with smaller BOLD signal changes. These results suggest that to avoid overestimation of the cerebral metabolic rate of oxygen changes seen using fMRI, caution should be taken to not include voxels with large veins and a large BOLD signal. Wu et al., Magnetic Resonance in Medicine, 48, pp. 987-993, 2002.

Cerebral Perfusion Imaging Using Arterial Spin Labeling at 1.5 and 4.0 Tesla

Detre and colleagues at the University of Pennsylvania compared arterial spin labeling (ASL) perfusion MRI using a pulsed ASL (PASL) technique at 4T with PASL and continuous ASL (CASL) techniques at 1.5T. ASL imaging was performed in normal subjects both in the resting state and during motor activation. Although in the resting-state the 4T PASL exhibited the greatest signal to noise and contrast to noise ratios, the functional data acquired using 4T PASL did not show significantly improved sensitivity to motor cortex activation compared with the 1.5T functional data. In addition, the 4T PASL exhibited reduced fractional perfusion signal change and increased intersubject variability. Wang et al., Magnetic Resonance in Medicine, 48, pp. 242-254, 2002.

GABAergic Mechanisms of Heroin-Induced Brain Activation

Li and colleagues at the Medical College of Wisconsin used fMRI in rats to test whether heroin activates dopamine projection cells by stimulating opiate receptors on inhibitory interneurons that inhibit gamma-aminobutyric acid (GABA) release. Acute, systemic administration of heroin produced a significant blood oxygen level-dependent (BOLD) signal increase in cortical regions, including prefrontal cortex, cingulate, and olfactory cortex. In contrast, a significant signal decrease was seen in several subcortical areas, including the caudate and putamen, nucleus accumbens, thalamus, and hypothalamus. Pretreatment with naloxone, eliminated and post treatment with naloxone reversed the heroin-induced BOLD signal changes. Pretreatment with gamma-vinyl GABA (GVG), an irreversible GABA transaminase inhibitor, significantly attenuated the heroin-induced BOLD signal changes. It is suggested that opiates' pharmacological actions can, at least in part, be mediated by inhibiting brain GABA release. Xi, et al. Magnetic Resonance in Medicine, 48, pp. 838-843, 2002.

Brain Dopamine D2 Receptors Predict Reinforcing Effects of Stimulants: Replication

Volkow and colleagues at the Brookhaven National Laboratory determined the replicability of previous findings characterizing the relationship between striatal dopamine (DA) D2 receptors and self-reports of "drug liking". PET scans were performed in seven, non-drug abusing subjects administered intravenous methylphenidate, a psychostimulant that acts like cocaine to increase DA by blocking DA transporters. Measures were taken twice to assess stability. Results were consistent with previous findings. DA D2 measures were significantly correlated with "drug liking" in both evaluations (r = 0.82, 0.78); subjects with the lowest levels of receptors reported the higher ratings of "drug liking", whereas those subjects with the highest levels of receptors reported consistently lower ratings of "drug liking". These results provide further evidence that striatal DA D2 receptors modulate reinforcing responses to stimulants in humans and may underlie predisposition for drug abuse. Also, these results provide evidence that high levels of DA D2 receptors may be protective for drug abuse. Finally, these results corroborate the involvement of DA D2 receptors in the perception of the reinforcing effects of psychostimulants in human subjects. Volkow, N.D., Wang ,G-J., Fowler, J.S., Thanos, P., Logan, J., Gatley, S.J., Gifford, A., Ding, Y-S., Wong, C., and Pappas, N. Brain DA D2 Receptors Predict Reinforcing Effects of Stimulants in Humans: Replication Study. Synapse, 46, pp. 79-82, 2002.

Childhood Emotional Neglect May Influence Monoamine Function in Adults

Childhood stress has been shown in animal models and implied in humans to influence the vulnerability to drug abuse in adults. Roy has demonstrated that

abstinent cocaine-abusing adults with retrospective reports of childhood neglect had low levels of both 5-HIAA, the metabolite of serotonin, and HVA, the metabolite of dopamine in significant correlation with symptom scores. Aggression and behavioral disorders, including suicide, are associated with low serotonergic function that may have developmental antecedents in childhood environment. The relevance to drug abuse vulnerability needs to be explored. Roy, A., Psychiatry Research, 112, pp. 69-75, 2002.

Dopamine Metabolite, HVA, in CSF Fails to Correlate with Cocaine Craving in Recently Abstinent Patients in Treatment

Roy and colleagues assessed 20 cocaine patients on a locked treatment ward for visually cued cocaine craving following lumbar puncture to determine the level of the dopamine metabolite, homovanillic acid and the serotonin metabolite, 5-hydroxy-indoleacetic acid. No correlation between either of these measures and craving scores was found. This was true when only the patients whose craving scores increased the most were compared with those whose scores did not change. These results must be considered in light of extant hypotheses regarding the role of dopamine in cocaine craving. Roy, A., Berman, J., Bienvenido G. and Roy, M. Journal of Psychopharmacology, 16(3), pp. 227-229, 2002.

P300 Event-Related Potentials Are Associated with Risk of Substance Abuse

Iacono and colleagues at the University of Minnesota have followed a population sample of twins and have now determined that P300 amplitudes are significantly smaller in at-risk adolescent offspringÐ those whose parents have a diagnosed alcohol or substance abuse or anti-social personality disorder. This was true whether or not the adolescent was or was not abusing substances or had a psychiatric diagnosis. Furthermore, adolescents who were not abusing drugs at age 17 but began abusing by age 20 had smaller P300 amplitudes than those who did not take drugs by age 20. Thus, not only is a lower amplitude P300 a possible biological marker for at-risk substance use based on father's diagnosis, but it is also predictive of who might become a drug abuser regardless of parental history. The authors suggest that the P300 may be an endophenotype underlying and common to a constellation of disorders including substance abuse but also including other externalizing disorders Ð conduct disorder, etc. Iacono, W.G., Carlson, S.R., Malone, S.M., and McGue, M. Archives of General Psychiatry, 59(8), pp. 750-757, August 2002.

Relationships Among Brain Metabolites, Cognitive Function, and Viral Load in Antiretroviral-Naive HIV Patients

Dr. Chang and her colleagues conducted an evaluation of antiretroviral-naive individuals that minimized the confounding effects of antiretroviral treatment on the relationship among cerebral metabolite concentrations, cognitive function, and clinical variables. Antiretroviral-drug-naive, HIV+ individuals (45) and control subjects (25) were tested. As measures of dementia severity increased, frontal lobe myoinositol concentration [MI], choline concentration [CHO], and total creatine [CR] were elevated, and basal ganglia [CR] was decreased. HIV+ patients showed slowing on fine motor and psychomotor function, and deficits on tests of executive function. Lower CD4 counts and elevated plasma viral loads were associated with elevated frontal white matter [MI], which in turn correlated with performance decrements on the Stroop tasks. These findings suggest that systemic factors may lead to glial proliferation in the frontal white matter, which in turn may contribute to deficits on executive function in HIV+ patients. Metabolite concentrations, rather than metabolite ratios, should be measured since [CR], a commonly used reference for metabolite ratios, varies with disease severity in both frontal lobe and basal ganglia. Chang, L. Ernst, T., Mallory D., Ames, N., Gaiefsky, M., and Miller, E. Relationships among Brain Metabolites, Cognitive Function, and Viral Loads in Antiretroviral-naive HIV Patients, NeuroImaging, 17(3), pp. 1638-1648, November 2002.

Neuropsychological Performance in Individuals Following Six Weeks or Six Months of Abstinence from Abuse of Crack-Cocaine or Crack-Cocaine Plus Alcohol

To evaluate the extent that crack dependence and crack and alcohol dependence may lead to severe and persistent neuropsychological deficits over a wide range of domains, Fein and colleagues at Neurobehavioral Research, Inc. examined cognitive function in abstinent crack-dependent and crack- and alcohol-dependent individuals at 6 weeks and 6 months abstinence. A comprehensive neuropsychological battery was administered to 20 abstinent crack-dependent subjects, 37 abstinent crack- and alcohol-dependent subjects, and 29 normal controls. Depression was examined as a

covariate, and the association between substance use variables and neuropsychological performance was examined. Both substance-dependent groups had similar neuropsychological profiles at 6 weeks abstinence, with both groups exhibiting significant cognitive impairment across a wide range of variables compared to the controls. The substance-dependent groups continued to show significant impairment after 6 months 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, V., Tolou-Shamas, M., Price, L.J., and Fein, G. Neuropsychological Performance of Individuals Dependent on Crack-Cocaine, or Crack-Cocaine and Alcohol, at 6 Weeks and 6 Months of Abstinence. Drug and Alcohol Dependence, 66(2), pp. 161-171, April 2002.

Prefrontal Cortical Volume Reduction Associated with Frontal Cortex Function Deficit in 6-Week Abstinent Crack-Cocaine Dependent Men

Fein and colleagues examined regional cortical volumes in 6-week abstinent men dependent on crack-cocaine (n=17) only or on both crack-cocaine and alcohol (n=29) to evaluate possible prefrontal cortical volume reduction, along with associated impairments in frontal-mediated functions, and to look for any differences between these groups. Magnetic resonance imaging (MRI) of the brain and neuropsychological assessment were performed on all dependent subjects who had been abstinent for six weeks as well as on 20 normal controls. Cortical volume was quantified in the prefrontal, parietal, temporal and occipital regions. The crack-only and crack-plus-alcohol subjects showed comparable reductions in prefrontal gray matter volume compared to the controls; this reduction was negatively associated with performance impairments in the executive function domain. Dependence on crack (with or without concomitant alcohol dependence) was associated with reduced prefrontal cortical volume. Crack dependence with concomitant alcohol dependence was not associated with greater prefrontal volume reductions than crack dependence alone. The existence of these findings at 6-week abstinence indicates that they are not a result of acute cocaine or alcohol exposure. The association of reduced prefrontal cortical volume with cognitive impairments in frontal cortex mediated abilities suggests that this reduced cerebral volume has functional consequences. Fein, G., DiSclafani, V., and Meyerhoff, D.J. Prefrontal Cortical Volume Reduction Associated with Frontal Cortex Function Deficit in 6-week Abstinent Crack-Cocaine Dependent Men. Drug and Alcohol Dependence, 68(1), pp. 87-93, September 2002.

Efficacy for CBT and CM

Dr. Richard Rawson and colleagues at UCLA Integrated Substance Abuse Programs compared contingency management (CM) and group cognitive behavioral therapy (CBT) to combined CM and CBT and usual care (methadone maintenance) as a treatment for patients with cocaine and opiate dependence. Urinalysis results one week after treatment show that participants assigned to the CM groups had significantly superior in treatment outcomes whereas those receiving CBT only were not more likely to be drug free in treatment than those in methadone maintenance alone. However, at the 26 week and 52 week follow-up all three groups outperformed methadone maintenance alone. Results of this study suggest that both CM and CBT alone and in combination are efficacious for reducing drug use 6 and 12 months after treatment completion. Rawson, R.A., Huber, A., McCann, M., Shoptaw, S., Farabee, D., Reiber, C., and Ling, W. A Comparison of Contingency Management and Cognitive-Behavioral Approaches during Methadone Maintenance Treatment for Cocaine Dependence. Arch. Gen. Psychiatry, 59(9), pp. 817-824, September 2002.

Dissemination of Contingency Management Methods

Dr. Nancy Petry at University of Connecticut School of Medicine reviewed recent advances in the dissemination of contingency management (CM) techniques including ways researchers have reduced costs by implementing programs based on intermittent schedules of reinforcement and clinic privileges. The review notes clinic needs often differ from the ways CM has been used in research. For example, clinicians report the need to reinforce abstinence from more than one drug of abuse, while research has typically focused on a single drug of abuse. The need for training programs for community clinicians is particularly noteworthy. The review highlights some of the ways in which findings from research can be implemented clinically and suggests that researchers and clinicians can learn from one another's experiences to bring CM procedures into practice and improve outcomes in the treatment of substance use disorders. Petry, N.M., and Simcic, F., Jr. Recent Advances in the Dissemination of Contingency Management Techniques: Clinical and Research Perspectives. J. Subst. Abuse Treat., 23(2), pp. 81-86, September 2002.

Smoking Cessation in Methadone Maintenance

Dr. Steve Shoptaw and colleagues at the Friends Research Institute evaluated the efficacy of relapse prevention and contingency management interventions for smoking cessation in methadone maintained patients in a 2 X 2 design using nicotine replacement therapy as a platform pharmacotherapy. One-hundred and seventy-five smokers received 12 weeks of NRT and were assigned to one of four conditions: 1) patch only; 2) relapse prevention + patch; 3) contingency management + patch; or 4) relapse prevention + contingency management + patch. During treatment, those assigned to receive contingency management showed statistically higher rates of smoking abstinence than those not assigned to receive contingencies. At follow-up there were no significant differences between conditions. Participants provided more opiate and cocaine-free urines during weeks when they met criteria for smoking abstinence than during weeks when they did not meet these criteria. The authors conclude that contingency management optimized outcomes using NRT for reducing cigarette smoking during treatment for opiate dependence, although long-term effects are generally not maintained. Findings document strong associations between reductions in cigarette smoking and reductions in illicit substance use during treatment. Shoptaw, S., Rotheram-Fuller, E., Yang, X., Frosch, D., Nahom, D., Jarvik, M.E., Raswon, R.A., and Ling, W. Addiction, 97(10), pp. 1317-1328, October 2002.

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

Researchers at Brown University and the Miriam Hospital examined whether length of alcohol abstinence and depressive symptoms were related to motivational readiness to consider smoking cessation among patients in alcohol treatment. Participants were 253 adults enrolled in a smoking cessation trial. Findings show that a greater number of days since last drink were associated with greater readiness to quit smoking, but only among patients with low scores on a depression scale. The findings suggest that alcoholic smokers with low depressive symptoms are more receptive to quitting smoking after sustained alcohol abstinence. Hitsman, B., Abrams, D.B., Shadel, W.G., Niaura, R., Borreli, B., Brown, R., Emmons, K.M., Swift, R.M., Monti, P.M., Rohsenow, D.J., and Coby, S.M. Psychology of Addictive Behaviors, 16(3), pp. 264-268, 2002.

Suicide Attempts in Substance Abusers: Effects of Major Depression in Relation to Substance Use Disorders

Dr. Aharonovich and colleagues at Columbia University in New York, investigated whether subtypes of DSM-IV depression predict suicidal behavior among patients with substance dependence. In this study, major depression among 602 patients with substance dependence was classified as occurring before dependence, during abstinence, or exclusively during periods of substance use. The findings indicate that all three types of depression increased the risk for making a suicide attempt. Major depression that occurred before the patient became substance dependent predicted severity of suicidal intent. Major depression that occurred during abstinence predicted number of suicide attempts. These results suggest the importance of establishing DSM-IV subtypes of depression based on the timing of the occurrence of depression in relation to substance dependence in evaluating suicidal risk among substance-dependent patients. Aharonovich, E., Xinhua, L., Nunes, E., and Hasin, D. American Journal of Psychiatry, 159, pp. 1600-1602, September 2002.

Substance Abuse and the Need for Money Management Assistance Among Psychiatric Inpatients

Dr. Marc Rosen and colleagues at the VA Connecticut Healthcare System, the VA Medical Center in Los Angeles, California, and the VA Bedford Medical Center in Massachusetts, evaluated the relationship between substance abuse and clinician-rated need for money management assistance, using data from a survey of psychiatric inpatients at four VA hospitals (N= 236). Multivariate analytic techniques were used to control for sociodemographic factors and psychopathology. Alcohol and drug use severity both were modestly associated with need for assistance. The effect of substance use severity was greater in patients who were also diagnosed with a major mental illness. Clinicians indicated that 27 patients (11% of the sample) required an involuntary payee and 21 of the 27 (78%) had a Substance Abuse diagnosis. Only drug use severity was significantly associated with the need for a payee. These data describe a substantial unmet need for money management assistance in psychiatric inpatients, particularly among those with substance abuse disorders. Patients who mismanage their funds may benefit from financial advice, case management, or the assignment of a payee who may restrict direct access to funds. Rosen, M., Rosenheck, R., Shaner, A., Eckman, T., Gamache, G., and Krebs, C.

Drug and Alcohol Dependence, 67, pp. 331-334, May 2002.

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

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

Relationship Among Gender, Depression, and Needle Sharing in a Sample of Injection Drug Users

The findings from this study replicate two prior and consistent findings: (a) Women are more likely than men to share needles, and sharers report higher levels of depression than non-sharers. Both of these findings are important in and of themselves; however, the finding that women who share needles reported the highest level of depression of all groups adds new information to the existing literature about this important public health issue. This suggests that the relationships among gender, depression, and needle sharing are more complex than previously assumed, especially for women. Johnson, M.E., Yep, M.J., Brems, C., Theno, S.A., Fisher, D.G Psychology of Addictive Behaviors, 16, pp. 338-341, 2002.

Drug Use, Travel, and HIV Risk

Studies have described how transmission of diseases is socially organized around geographic travel and migration patterns. Sexual and other risk behaviors while traveling abroad have been examined and considered as causal factors in the spread of HIV infection and other STDs. The spread of HIV/AIDS into rural areas has also been linked to high-risk behaviors of rural residents who frequently travel into urban areas. In this study, researchers examined the travel experiences of a community sample of 160 drug users and 44 non-users recruited as part of a social network study of HIV risk. Of the sample, 47% (96 of 204) reported intercity travel in the prior 2 years. Results showed that men were more likely to travel than women, Anglos more than minorities, and young persons more than old. When travelers testing HIV-positive (n=13) were compared with HIV-negative travelers, HIV-positive travelers reported more safe sex (condom use) and more sex partners while traveling than HIV-negative persons. There were no significant differences in sex risk behaviors while traveling between drug users and non-users, or in sex behaviors between IDUs and non-IDUs. Travelers had fewer injection partners while traveling than they had while at home. However, drug-using travelers had a higher rate of drug injection and tended to take longer trips than non-drug users. There was also a significant difference in number of sex partners with whom a condom was not used. At home, there were more sex partners with whom a condom was not used compared to while traveling. Overall, however, this study found that persons who regularly engaged in risky behaviors were not more likely to travel, indicating that more HIV transmission occurs within cities than between cities. Lee, D., Bell, D., and Hinojosa, M. Drug Use, Travel, and HIV Risk. AIDS Care, 14(4), pp. 443-453, 2002.

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

A feasibility study was conducted to determine whether a peer-driven intervention that was first developed as an HIV prevention mechanism for drug users could be adapted to improve HIV+ drug users' health seeking behaviors. Fifteen HIV+ IDUs were recruited, and 14 were accepted into the study. The feasibility study deliberately sought the most challenging subset of HIV+ IDUs Ð i.e., active IDUs who had prior enrollment in HIV care but, based on a clinician's perceptions, were poorly adherent. Each subject served as a health advocate to a peer of the same sex, and met with the peer once a week to assess how well the peer was keeping up with his or her medical care. Each subject also participated as a peer being served by another health advocate. Results suggest that HIV+ drug users are willing and able to play active roles in helping one another to keep up with their medical treatments. The 14 peers

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kept 84% of their appointments with primary care providers and HIV-related support services. Altogether, only seven appointments were missed. Although it was not a goal of the study, drug-related HIV risks (sharing syringes and equipment specifically) were found to decrease during the study from 36% to 7%. The researchers conclude from the study that an alternative social support structure to drug treatment is feasible for increasing active drug users' adherence to medical care. Broadhead, R., 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 Science and Medicine, 55, pp. 235-246, 2002.

Religious Behaviors and HIV-Related Health Care Among IDUs in Baltimore

In many communities, religious institutions are important sources of social support and integration. This study was conducted to examine the relationship among religious behavior and HIV testing, HIV serostatus, and HIV medical care among 1,568 inner-city former and current IDUs in Baltimore, Maryland. Overall, 93% of the participants reported previous HIV testing. About 46% attended church in the past month. Religion or spirituality providing at least some guidance in day-to-day living was reported by 85%. Current drug use was negatively associated with church attendance yet 40% of the active drug users had been to church in the past month and 67% in the past year. There was a significant association between HIV testing and recent church attendance, and participants who reported that they were positive for HIV had higher rates of recent church attendance. Participants who reported currently receiving medical care for HIV were more likely to have attended church recently and more likely to report that religion or spirituality provided them with guidance in their daily lives. This study found that church attendance is frequent and religion is a strong source of guidance among impoverished inner-city drug users. The findings suggest that HIV prevention and treatment strategies that build on prior religious experiences may be useful for this population, for example by incorporating concepts that involve shared behavioral experiences to link HIV prevention, testing, and medical treatment into their histories and social context. Latkin, C., Tobin, K., and Gilbert, S. Shun or Support: The Role of Religious Behaviors and HIV-Related Health Care Among Drug Users in Baltimore, Maryland. AIDS and Behavior, 6(4), pp. 321-329, 2002.

Self-Reported NEP Attendance Among IDUs: Implications for Program Evaluation

Some studies have indicated that needle exchange programs (NEPs) can be effective in reducing drug-related risks for HIV seroconversion, while others have reported higher HIV incidence rates among NEP attendees. Since many studies rely on self-reports of NEP evaluation, researchers investigated the extent to which differential misreporting of NEP attendance could bias risk estimates. That is, they explored the biases that can result from misclassification of exposure assessment and how this can mask true underlying associations between NEP attendance and HIV seroconversion. Over a 3-year period, from 1994 to 1997, self-reports of NEP attendance from participants in a prospective study in Baltimore, MD, were compared with NEP records. Of 1,315 participants, 459 (35%) had registered with the Baltimore NEP. There was 86.7% concordance between self-reported and actual NEP use; 11.0% reported NEP attendance but did not attend (over-reported), and 2.2% reported not attending NEP but did attend (under-reported). In multivariate analyses using generalized estimating equations, persons who over-reported NEP attendance were more likely to have injected frequently, denied needle sharing, and been an HIV seroconverter. With Poisson regression to model predictors of HIV seroconversion, models that included measures of NEP attendance based on self-reports compared with actual program data underestimated a protective association by 18%. From the perspective of evaluating an HIV prevention program, over-reporting of NEP use, particularly among high-risk persons who are at higher risk of HIV, can seriously underestimate the negative association of NEP with HIV seroconversion, especially if the true association is relatively modest. Safaeian, M., Brookmeyer, R., Vlahov, D., Latkin, C., Marx, M., and Strathdee, S. Validity of Self-Reported NEP Attendance Among IDUs: Implications for Program Evaluation. Am. J. Epidemiol., 155(2), pp. 169-175, 2002.

Alcohol Use Among Out-of-Treatment Crack-Using African American Women

This study categorized the quantity and frequency of alcohol use among African American women who were abusing crack cocaine to explore relationships between categories of alcohol use, demographic variables, cocaine use, co-morbidity, and risky sexual behaviors. Data were collected from 635 out-of-treatment crack cocaine using

women in Raleigh/Durham, North Carolina. The women were categorized as light (n=272, 43%), moderate (n=216, 34%) or heavy drinkers (n=147, 23%). The groups were similar in age distribution and marital status. Women classified as heavy drinkers were demographically similar to light and moderate drinkers. Heavy drinkers used more crack cocaine, reported longer crack runs (24 hours or longer in length), and were more likely to engage in sexual risk behaviors, including exchanging sex for drugs, money, or shelter, compared to the other two drinking groups. The heavy drinkers also reported greater psychological distress, including anxiety and post-traumatic stress, and were more likely to report histories of physical, sexual, and emotional abuse. Heavy alcohol use among crack-abusing African American women may be a marker for a host of underlying problems that require special attention. The HIV prevention programs and substance abuse treatment programs that provide services to crack-abusing women should screen for heavy drinking. Women identified as heavy drinkers should undergo more in-depth assessments and receive additional referrals as appropriate. Zule, W., Flannery, B., Wechsberg, W., and Lam, W. Alcohol Use Among Out-of-Treatment Crack-Using African American Women. Am J Drug Alcohol Abuse, 28(3), pp. 525-544, 2002.

Social Networks and Forecasting the Spread of HIV Infection

Researchers used network data to forecast the spread of HIV in a large U.S. city. Data were collected from a sample of drug users and socio-demographically matched nonusers in low-income areas of Houston, Texas. Two sample-based HIV prevalence models and two sociological models were combined with three published biological models to yield forecasts of the growth of HIV seroprevalence. The forecasts predict a compounded annual growth in HIV of between 2.4% and 16.5% among low-income residents of Houston's inner city. Accurately forecasting the growth of HIV/AIDS is critical to policy makers, researchers, and clinicians. This study evaluated the relative sensitivity of HIV projections by producing a range of forecasts using 3 hypothetic biological models that were combined with two empiric prevalence models and an empiric sociological model. Results showed that the greatest sensitivity was in the sociological models and that random mixing models, even those that maintain individual levels of activity, tend to overestimate HIV transmission by a factor of 3. The collection of additional social network data is probably the most important requirement for more accurate projections. Bell, D.C., Montoya, I., Atkinson, J.S., and Yang, S. Social Networks and Forecasting the Spread of HIV Infection. J Acquired Immune Deficiency Syndromes, 31, pp. 218-229, 2002.

Syphilis Among IDU Populations in St Petersburg, Russia

An epidemic of syphilis and other STDs in the Russian Federation is believed to be related to the rise in injection drug use. A study was carried out in collaboration with a nongovernmental Russian charity organization, Foundation Vozyrastcheniye ("Return"). The program was aimed at providing medical, social, and educational assistance to IDUs in St Petersburg. It was carried out in the form of a special mobile medical unit where doctors and nurses were able to offer basic medical assistance that included exchange of syringes, drug abuse, STD and infectious disease counseling, and screening blood samples for HIV, syphilis, and hepatitis seromarkers. Nine hundred and ten IDUs participating in the program were tested for syphilis, HIV, HCV, and HBV. Sixty-five participants who had laboratory markers for syphilis and 45 syphilis-negative subjects agreed to participate in a questionnaire study. The results indicated that syphilis, HIV, HBV, and HCV were diagnosed in 12%, 0%, 48%, and 79% of drug users respectively. Prevalence of syphilis seromarkers was nine times higher in females than in males, and highly correlated with sex work. The fact that sex workers in particular would continue to have unprotected sex while having syphilis infection suggests that there may be an economic or other motive for having sex without a condom. Syringe sharing was also common in this population, suggesting the possibility of syphilis transmission via this route of exposure. These results suggest that resources to treat and prevent further infections including HIV should be directed toward risk reduction in IDUs and sex workers in St. Petersburg. Karapetyan, A., Sokolovsky, Y., Araviyskaya, E., Zvartau, E., Ostrovsky, D., and Hagan, H. Syphilis Among IDU Populations: Epidemiological Situation in St. Petersburg, Russia. International J STD & AIDS, 13, pp. 618-623, 2002.

Resource Acquisition Strategies of Inner City Women Who Use Drugs

To better understand how women's HIV risk is influenced by environmental factors, researchers conducted life history interviews and assessed the strategies women adopted for acquiring resources (resource acquisition strategies), as well as the costs and obligations associated with such strategies. Interviews were conducted with 28 women who used drugs in two low-income neighborhoods in New York City. The

women were 18 years and older, used heroin, crack, or cocaine, and were recruited from out-of-treatment settings between March and November 2000. The majority of women's resources came from illegal sources or from men with whom they had sexual relationships. Three fourths of the women worked in the drug trade, 68% reported stealing and 68% engaged in street based sex work. Most (89%) women had been arrested. The large majority (79%) had current, male sex partners, from whom they received financial and other benefits, including a diminished risk of incarceration. The implicit or explicit trade of sex for a reliable supply of resources severely limited women's ability to implement sex risk reduction. Avoidance of incarceration, primarily for drug-related offenses, as well as access to substantial and varied resources required both for drug use and for daily survival, favored acquiring resources through establishing sex partnerships with men who could supply at least some level of resources. In the context of economic deprivation, most resource acquisition strategies employed by the women increased HIV risks. Miller, M. and Neaigus, A. An Economy of Risk: Resource Acquisition Strategies of Inner City Women Who Use Drugs. International J Drug Policy, 13(5), pp. 399-408, 2002.

Drug Users' Involvement in the Drug Economy

Researchers examined individual and social characteristics associated with drug users' involvement in the drug economy among a sample of low-income heroin and cocaine users (n=1,288) in Baltimore, MD. The study sample had participated in a network-oriented intervention study of HIV risk behaviors among drug users. Of the sample, 44% (n=569) held at least one role in the drug economy, performing an average of 1.17 roles. A significantly higher percentage of those involved in the drug economy reported being daily drug users (60.6% vs. 40.2%), injecting heroin daily (36.0% vs. 21.8%), injecting speed daily (23.6% vs. 14.7%), and snorting heroin daily (18.3% vs. 13.4%). In terms of social networks, those involved in the drug economy reported a significantly larger social network (9.98 vs. 8.97), greater percentage of active drug users in their social network (47% vs. 44%), greater percentage of active daily drug users in their social network (40% vs. 33%), and larger drug support networks (6.7 vs. 5.6). Drug users involved in the drug economy were significantly more likely to perceive worse withdrawal symptoms and to worry more about getting sick. The study indicates the far-reaching influence of drug use on many aspects of their lives, including their involvement with the drug economy. Reducing drug users' frequency of use could have the consequence of decreasing this involvement. Being a part of the drug economy exposes drug users to many risks, but also places them in a position to influence others. Examining drug users' social networks could provide insights into the composition of their immediate social environment and could inform HIV prevention programs. Sherman, S. and Latkin, C. Drug Users' Involvement in the Drug Economy: Implications for Harm Reduction and HIV Prevention Programs. J Urban Health, 79(2), pp. 266-277, 2002.

Sex Partner Support, Drug Use, and Sex Risk Among Non-Injecting Heroin Users

Researchers examined the extent to which sex partner characteristics, including partner support, influence HIV risk practices among HIV-seronegative non-injecting heroin users. The sample (n=257) was racially/ethnically diverse and predominantly male. More than two-thirds of the respondents reported using heroin with other people in the past 30 days and 30% reported using heroin with sex partners. Three-quarters reported having unprotected sex within the past 30 days; 27% had sex with partners at known risk of being HIV infected. There were no gender differences in terms of sex or drug use practices, but there were differences in sex partner characteristics. Men were significantly less likely than women to have partners who used drugs, receive support from their partners, use heroin with their partners, and have partners at known risk of being HIV infected. For men, increased sex risk was independently associated with having used heroin with sex partners. Women were just as likely to have unprotected sex with partners who provided support as with partners who did not. Moreover, women's partners appeared to pose greater HIV sex risk than men's partners. A disturbing finding was that an awareness of a known increase in HIV risk posed by sex partners was not associated with increased consistent condom use for either men or women. In this analysis, sex partner support was found to discriminate between men who reported unprotected sex and those who did not. Social support may have detrimental as well as beneficial consequences on HIV risk. Miller, M. and Neaigus, A. Sex Partner Support, Drug Use and Sex Risk Among HIV Negative Non-Injecting Heroin Users. AIDS Care, 14(6), pp. 801-813, 2002.

Hepatitis Knowledge is Low and Risks Are High Among IDUs in Three U.S.

Cities

In this study, researchers examined the interrelationships among HIV and hepatitis knowledge, risky drug preparation and injection practices, and participation in syringe exchange programs (SEPs) in inner-city neighborhoods of Chicago, Hartford, and Oakland. The study population was a convenience sample of 493 IDUs recruited using street outreach and snowball sampling strategies. Interviews were conducted using a semi-structured questionnaire adapted from the NIDA Risk Behavior Assessment, with measures of hepatitis and HIV knowledge, injection-related risks for virus transmission, associations between the two, and with SEP use. The study found that HIV knowledge was significantly higher than hepatitis knowledge among SEP customers and non-customers alike. A corollary to the lack of knowledge about hepatitis was the finding that many IDUs are unaware that they have been infected with hepatitis. Elevated hepatitis knowledge was associated with a history of substance abuse treatment, hepatitis infection, hepatitis B vaccination, and injection practices that reduced contact with contaminated blood or water but not with SEP use. SEP customers were consistently less likely to engage in risky syringe practices, including syringe re-use and sharing water for drug preparation and syringe rinsing, compared to non-customers. However, SEP users were 2x likelier to staunch blood flow following injection, using alcohol wipes. This places them at higher risk of exposure to blood because isopropyl alcohol inhibits clotting. SEPs need to disseminate information that alcohol wipes should only be used to clean the skin before injection. In this study, increased hepatitis knowledge was not associated with SEP use, but instead with a diagnosed hepatitis infection. These findings suggest that SEPs must also do more to increase hepatitis awareness and prevent hepatitis transmission among IDUs. Heimer, R., Clair, S., Grau, L., Bluthenthal, R., Marshall, P., and Singer, M. Hepatitis-Associated Knowledge is Low and Risks are High Among HIV-Aware IDUs in Three US Cities. Addiction, 97, pp. 1277-1287, 2002.

Syringe Type and Drug Injector Risk for HIV Infection: A Case Study in Texas

Studies of accidental needle stick exposure to HIV-infected blood have shown that the volume of blood in an exposure is a strong predictor of subsequent infection. Injecting drug users use syringes manufactured in two styles, one of which (the integral cannula type) retains substantially less blood after intravenous use than the other (the detachable needle type). Researchers examined some of the factors associated with use of syringes with detachable needles among IDUs in San Antonio, Texas using data from epidemiological surveys, ethnographic studies, and historical observations. They compared history of syringe type use with HIV serostatus in a sample of 501 active IDUs interviewed and screened for HIV in 1997-1998. Ninety-nine percent of these respondents reported that they currently used only integral cannula syringes, but 13% had used a syringe with a detachable needle within the past 2 years, and 37% had used one in their lifetime. Only 9% had ever used one > 20 times in a year. Hispanic (Mexican American) respondents were significantly less likely than other ethnic groups to have ever used a detachable needle syringe. HIV seroprevalence was < 1% among heterosexual IDUs who had never used a detachable needle syringe compared to 4% among those who had used one. Zule, W., Desmond, D., and Neff, J. Syringe Type and Drug Injector Risk for HIV Infection: A Case Study in Texas. Social Science and Medicine, 55, pp. 1103-1113, 2002.

Transmission/Prevention of HIV/STIs in War Settings: Implications for Armed Conflicts

Researchers reviewed the effects of war on HIV/STI transmission and appraised short- and medium-term approaches to prevention. Armed conflicts can influence HIV epidemic dynamics in surrounding countries and beyond, both directly by affecting HIV transmission itself and indirectly through reallocation of health-related public funds toward security and defense measures. Poverty, powerlessness, and social instability, all of which facilitate HIV transmission, are magnified during complex emergencies, but HIV is rarely seen as a priority. During World Wars I and II and in more recent conflicts, high rates of STI were recorded in the military. Changing patterns of sexual behavior, drug use, and increased HIV/STI risk were found in 1998 among young people displaced by the war in Bosnia-Herzegovina. War-related fluctuations in drug supply can lead to widespread HIV transmission in areas of drug transit, as some local residents start taking drugs because of increased drug availability or payment in kind for services rendered. In such situations, which do not lend themselves to safer injection behaviors, other potentially fatal diseases, including hepatitis B and C, can spread among drug injectors and their partners. Large proportions of heroin users in Europe and the US have smoked or snorted the drug since the mid-1980s. Drug market fluctuations may lead significant numbers of them

to begin injecting. Moreover, in light of recent events, IDUs in Afghanistan are at particularly high risk of acquiring HIV. This concern is heightened in light of a study reported at the International AIDS Conference in July 2002 that found that, of 143 Afghan drug users in Quetta, Pakistan, none had ever used condoms. The authors discuss the implications of armed conflicts on public health, and identify a range of preventive intervention steps that can be taken to address immediate risks. Hankins, C., Friedman, S., Zafir, T., and Strathdee, S. Transmission and Prevention of HIV and Sexually Transmitted Infections in War Settings: Implications for Current and Future Armed Conflicts. AIDS, 16, pp. 1-8, 2002.

Hepatitis C and Substance Use in a Sample of Homeless People in NYC

Researchers examined the prevalence of hepatitis C antibodies and its association with substance use and sexual behavior among a sample of 139 persons visiting a mobile medical clinic in Manhattan. Ninety percent were unstably housed or were living on the street. The prevalence of HCV antibodies was 32%. Prevalence was also high for hepatitis B core antibodies (47%), HIV antibodies (15%), and syphilis exposure (14%); 76% tested positive for cocaine. Among those who reported ever injecting drugs (20%), 86% were HCV positive; 19% of non-IDUs were HCV positive. In separate logistic regression models that controlled for injection, HCV was predicted by quantitative hair assays for cocaine and self-reported duration of crack cocaine use. There was a clear dose response association of HCV and cocaine use in these results. Alcohol dependence and sexual behavior did not predict HCV. HCV is a significant public health problem among the urban homeless population, with injection drug use and to a lesser extent, cocaine use implicated as risk factors. Rosenbaum, A., Nuttbrock, L., McQuistion, H., Magura, S., and Joseph, H. Hepatitis C and Substance Use in a Sample of Homeless People in New York City. J Addictive Diseases, 20(4), pp. 15- 25, 2002.

Metabolic Abnormalities in HIV Disease and Injection Drug Use

HIV infection is associated with a number of adverse consequences, including metabolic disorders. This article reviews disorders such as wasting, lipid metabolism disorders (including fat redistribution or dyslipidemia), glucose abnormalities, bone disease, and endocrine disorders such as hypogonadism in the presence of HIV infection and/or drug abuse. The issues covered are current estimations of prevalence, risk factors, underlying pathophysiology, diagnosis, and interventions (prevention and treatment) for metabolic complications of HIV and drug abuse Dobs, A., and Brown, T. JAIDS, 31, Suppl 2:S70-S77, 2002.

Adherence to Anti-retroviral Therapy and Viral Load in HIV-infected Drug Abusing Women

Based on results from a prospective observational study of a cohort of HIV-infected drug abusing women in Bronx, NY, Dr. Howard and her colleagues of Montefiore Medical Center/Albert Einstein College of Medicine, report that adherence to antiretroviral therapy is not stable over time and that interventions aimed at monitoring and improving long-term adherence in this population are urgently needed. In a cohort of 161 women studied, about 25% of women had a 10% or greater decrease in adherence between consecutive months. Virologic failure occurred in 17% women with adherence greater than 88%, 28% of those with 45-87% adherence, 43% of those with 13-44% adherence, and 17% of those with less than 12% adherence. Factors such as active drug/alcohol use, shorter duration and more frequent antiretroviral dosing, younger age, and lower initial CD4 lymphocyte count predicted poor adherence. Howard, A.A., Arnsten, J.H., Yungtai, L., Vlahov, D., Rich, J.D., Schuman, P., Stone, V.E., Smith, D.K., and Schoenbaum, E.E. A Prospective Study of Adherence and Viral Load in a Large Multi-Center Cohort of HIV-infected Women, AIDS, 16, pp. 2175-2182, 2002.

HIV and Drug Abuse in the Edinburgh Cohort

The Edinburgh cohort of intravenous drug users (DU) became infected with human immunodeficiency virus (HIV) in 1983/84. Before the era of effective therapy, many of these infected DU displayed cognitive impairments progressing to AIDS and were found to have HIV encephalitis (HIVE). Full autopsies were conducted on these patients, providing an opportunity to study the intersecting pathology of pure HIVE and of drug use. High proviral load in the brain correlated well with the presence of giant cells and of HIV p24 positivity. In presymptomatic HIV infection, drug users were found to have a lymphocytic infiltrate in the central nervous system (CNS). Apart from the expected microglial activation in the presence of HIV infection of the CNS, drug use in its own right was found to be associated with microglial activation.

Examination of HIV negative drug users revealed a number of neuropathological features including microglial activation which may underpin HIV-related pathology in the CNS. Bell, J.E., Arango, J.C., Robertson, R., Brettle, R.P., Leen, C., and Simmonds, P. JAIDS, 31[suppl.2]: S35-S42, 2002.

Neuroprotection in HIV+ Drug Users: Implications for Antioxidant Therapy

Impaired neuroprotection, due to oxidative stress, has been implicated in neurodegeneration in a number of pathological conditions of the brain including both subcortical and cortical type dementias. Production of excessive oxidative stress, moreover, can lead to elevated levels of certain proinflammatory cytokines, that are considered to be contributing factors to neuronal injury, and are evident in HIV-related dementia, as well as other neurodegenerative conditions. Inhibitors of oxidative damage could, thus, be promising therapeutic agents for preventing progressive nerve cell death and slowing the advance of neurodegenerative disease. The potential of antioxidant therapy to provide neuroprotection is substantiated by studies demonstrating reduced oxidative stress with supplementation and lower risk for cognitive impairment with higher plasma antioxidant levels. Shor-Posner, G., Lecusay, R., Miguez-Burbano, M-J., Morales, G., and Campa, A. JAIDS, 31(suppl 2): S84-S88, 2002.

Ketamine Injection among High Risk, Street Involved Youth in New York City

Using ethnographic methods, investigators examined 25 young ketamine injectors in New York City. The following practices associated with ketamine injection were identified as risk factors for viral transmission of bloodborne pathogens, such as HIV, HBV, and HCV: (1) ketamine was typically injected in a group setting with up to 10 other injectors; (2) it was typical to inject multiple times, such as 8-10 times over several hours; (3) over half of the participants reported some form of paraphernalia sharing, including syringes and bottles; (4) a large proportion of participants received syringes from indirect sources; and (5) ketamine was frequently obtained for free which often led to spontaneous injection events. Their findings also suggest that, although ketamine is classified as a "club drug," the injection of ketamine occurs in a variety of settings and is typically injected and experienced apart from the club and rave scenes. The investigators conclude that ketamine injection is an emerging trend among hidden populations of injection drug users, particularly among high risk, street-involved youth. Lankenau, S.E. and Clatts, M.C. Ketamine Injection among High Risk Youth: Preliminary Findings from New York City. Journal of Drug Issues, 32, pp. 893 Ð 905, Summer 2002.

High Risk Drug Use Sites, Meaning and Practice: Implications for AIDS Prevention

This study presents preliminary findings of drug use in Hartford, CT, to understand the environmental and social conditions with "high-risk sites" where drug users inject drugs or smoke crack, in order to develop AIDS prevention models that build upon the physical and social organization of these locations. By understanding the environmental and social conditions within "high risk sites" where drug users inject drugs or smoke crack, the investigators are able to develop AIDS prevention models that build upon physical and social organization of these locations. A combination of ethnographic, epidemiological, and social network methods are used to document the characteristics, social organizations, natural history, and dynamics of the types of sites used, the network relations of site users, and the various opportunities for, or barriers to, on-site social-level HIV prevention intervention. Weeks, M., Clair, S., Singer, M., Radda, K., Schensul, J., Wilson, D., Martinez, M., Scott, G., and Knight, G. Journal of Drug Issues, 31(1), pp. 781-808, 2002.

An Ethno-Epidemiological Model for the Study of Trends in Illicit Drug Use: Reflections on the 'Emergence' of Crack Injection

National and regional tracking systems along with data from institutionally-derived sources (e.g. emergency departments, drug treatment admissions, and law enforcement data on drug seizures and arrests), have served as a source of sentinel markers about changes in drug use and its consequences. Sentinel marker data can be limiting because they typically fail to capture a number of "hidden populations" evidencing "hidden" drug-related risk behaviors such as patterns of episodic use evidenced in crack injection. This research study incorporates ethnographic methods, including field-based community assessment, semi-structured qualitative interviews, and targeted observation of "natural" venues in which drugs are bought, sold, and used, have potential to overcome some of the limitations from which "systems data" often suffer. Drawing on an ethno-epidemiological approach, the ongoing multi-site

research on the use of injection as a mode of administration in the use of crack cocaine is a case in point, and illustrates the potential utility of an ethnographic model for the identification and tracking of emergent and ongoing drug use practices. Clatts, M., Welle, D., Goldsamt, L., and Lankenau, S. International Journal of Drug Policy, 13, pp. 285-295, 2002.

Hepatitis C and Progression of HIV Disease

Conflicting reports exist regarding the impact of hepatitis C virus (HCV) infection on progression of HIV disease. A recent study by researchers at Johns Hopkins University assessed the effects of HCV infection on clinical and immunological progression of HIV disease and immunological response to highly active antiretroviral therapy (HAART) therapy among 1995 HIV-infected patients enrolled in an urban university-based HIV clinic. Median length of follow-up was 2.19 vs. 2.00 years for HCV-infected vs. HCV uninfected patients. No differences were observed in the risk of acquiring an AIDS-defining illness among HCV-infected patients vs. HCV-uninfected patients (231 vs. 164 AIDS-defining events; relative hazard (RH) =1.03) or in survival (153 deaths among HCV-infected patients vs. 168 deaths among HCV-uninfected patients, RH= 1.05). Among a subgroup of HCV-infected patients with low baseline CD4 cell count (between 50 and 200/microL), death was not independently associated with HCV infection after controlling for exposure to effective HAART. Among all patients receiving effective HAART (n=208), there was no difference in increase in CD4 cell count or CD4 percentage by HCV infection status. The authors conclude that in this urban cohort HCV infection was not observed to significantly alter risk of developing AIDS or death, or immunologic response to HAART when differences in its administration and effectiveness were accounted for. Sulkowski, M.S., Moore, R.D., Mehta, S.H., Chaisson, R.E., and Thomas, D.L. JAMA, 288, pp. 241-243, 2002.

Condom Use Among Drug-Using Youth in a High HIV-risk Neighborhood

Friedman and colleagues interviewed 196 18-24 year olds living in Bushwick, New York City, who injected drugs or used heroin, cocaine or crack in the prior year with the objective of assessing predictors of consistent condom use in heterosexual relationships in a high HIV-risk environment. Consistent condom use was reported in 26% of 277 non-commercial relationships and in all of 22 commercial relationships. Consistent condom use is more common in relationships that are described as not "very close" for men (but not women) with peers whose norms are more favorable to condom use, and for subjects who had concurrent sex partners in the last 12 months. The authors conclude that: (1) the lack of relationship between the peer norms of drug-using women and their condom use suggests that they may have little control over condom use in their relationships and this indicates a need for the development of programs to empower young female drug users; (2) the positive association of concurrency to consistent condom use suggests that condom use may be restricting HIV spread in the community and the presence of consistent condom use in all of the commercial sexual relationships may also restrict HIV spread; and (3) prevention efforts should attempt to change peer cultures as a way to develop self-sustaining risk reduction. Friedman, S.R., Flom, P.L., Kottiri, B.J., Neaigus, A., Sandoval, M., Fuld, J., Curtis, R., Zenilman, J.M. and Des Jarlais, D.C. Consistent Condom Use Among Drug-using Youth in a High HIV-risk Neighborhood. AIDS Care. 14(4), pp. 493-507, 2002.

Women, Sex, and HIV: Social and Contextual Factors, Meta-Analysis of Published Interventions, and Implications for Practice and Research

This article is focused on examining social and contextual factors related to HIV-risk behavior for women. Specifically, this article reviews: (1) the literature on selected social and contextual factors that contribute to the risk for the heterosexual transmission of HIV and AIDS, (2) reviews and conduct a meta-analysis of HIV-prevention interventions targeting adult heterosexual populations, and (3) suggests future directions for HIV-prevention intervention research and practice. Results suggest that the HIV-prevention interventions reviewed for this article had little impact on sexual risk behavior; that social and contextual factors are often minimally addressed; and that there was a large gap between research and the practice of HIV-prevention intervention. Logan, T.K., Cole, J., and Leukefeld, C. Women, Sex, and HIV: Social and Contextual Factors, Meta-analysis of Published Interventions, and Implications for Practice and Research. Psychological Bulletin, 128(6), pp. 851-885, 2002.

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

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

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

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

Prenatal Drug Exposure: Early Developmental Effects

Findings from the Maternal Lifestyle Study (MLS) show that prenatal cocaine effects at 1 month of age are detectable and subtle. In addition, the analyses demonstrate that the effects of other drugs (opiates, alcohol, marijuana) can also be observed in the context of a polydrug use model. The sample consisted of 658 exposed and 730 comparison infants matched on race, gender, and gestational age. Sites were located in Detroit, Memphis, Miami, and Providence. Cocaine exposure was related to lower arousal, poorer quality of movement and self-regulation, higher excitability, more hypotonia, and more nonoptimal reflexes, with most effects maintained after adjusting for covariates. Some acoustic cry characteristics, reflecting reactivity, respiratory, and neural control of the cry sound were also compromised by prenatal drug exposure (cocaine, opiates, alcohol, and marijuana). The researchers emphasize that the effects are subtle, i.e., reliable but small differences between the groups, not necessarily clinically significant deficits. However, the authors also emphasize that these subtle differences suggest neurobehavioral vulnerability that may be exacerbated by the caregiving environment, with the resulting potential to develop into deficits. In addition, there are long-term implications of the findings (e.g., cocaine may affect areas of the brain with consequences not likely to be seen until school age and beyond). Long-term follow-up is necessary for determining whether these subtle differences develop into clinically significant deficits. Lester, B.M., Tronick, E.Z., LaGasse, L, et al. The Maternal Lifestyle Study: Effects of Substance Exposure During Pregnancy on Neurodevelopmental Outcome in 1-Month-Old Infants. Pediatrics, 110, pp. 1182-1192, 2002.

Prenatal Cocaine Exposure and Child Language Functioning to 7 Years of Age

Dr. Emmalee Bandstra and colleagues at the University of Miami have reported new findings indicating a stable cocaine-specific effect on indicators of language functioning during early childhood through 7 years of age. Language functioning was assessed at ages 3, 5, and 7 years of age. The sample included 443 children (236 prenatally-exposed to cocaine, and 207 not exposed to cocaine). Longitudinal Generalized Linear Model and Generalized Estimating Equations (GLM/GEE) analyses indicated an association between prenatal cocaine exposure and deficits (i.e., about 1/5 standard deviation) in total language standard scores, after controlling statistically for gender of child; visit age; prenatal exposure to alcohol, marijuana, and tobacco; and over 20 potentially confounding medical and sociodemographic covariates. The researchers report that the link from prenatal cocaine exposure to later language deficits does not appear to be mediated by cocaine-associated deficits in birth weight, length, or head circumference. Bandstra, E.S., Morrow, C.E., Vogel, A.L., et al. Neurotoxicology and Teratology, 24, pp. 297-308, 2002.

Staphylococcus Aureus Infection in Drug Abusers

Lowy and his colleagues of Columbia University report that drug users have a higher incidence of colonization with *S.aureus* than does the general population and as a result are at high risk of infection, and in particular, colonization with similar bacterial isolates of *S.aureus* among inhalation drug users within drug-use risk networks. Their study suggests that patterns of drug use and the geographic location where drug sharing occurs are major contributors to the transfer of staphylococci and, as a result, to the high prevalence of staphylococcal colonization and perhaps disease in this

population (Clinical Infectious Diseases, 35, pp. 671-677, 2002). The investigators also maintain that there is limited understanding of the epidemiology and pathogenesis of *S.aureus* infection in drug users, partly due the difficulty of studying disease transmission among drug users in the community, and the limitations of the investigative tools that have been used. Based on an extensive review of the literature, the authors suggest that molecular epidemiological techniques and social network methodology should be used to understand the basis of the persistence, distribution, and transmission dynamics of *S. aureus* among drug users. In this paper they propose a framework for investigating the transmission of pathogens in community-based settings. Lowy, F.D. and Miller, M., New Methods to Investigate Infectious Disease Transmission and Pathogenesis-*Staphylococcus aureus* Disease in Drug Users, The Lancet, 2, pp. 605-612, 2002.

Cocaine and TB in Drug Users

Howard and her colleagues (Montefiore/Einstein Medical College, NY) report for the first time that cocaine use is one of the risk factors for tuberculin positivity in a community-based cohort of drug users in methadone treatment. In a cohort of about 800 current and former drug users, crack cocaine and alcohol use was associated with an elevated risk of tuberculin positivity. It was more evident in those infected with HIV, drug users who worked as home health aids, elderly, those born in Puerto Rico or a foreign country, and those who had contact with someone with active tuberculosis. The investigators recommend all drug users continue to be targeted for tuberculin testing in accordance with the current CDC guidelines. Howard, A.A., Klein, R.S., Schoenbaum, E.E., and Gourevitch, M.N. Crack Cocaine Use and Other Risk Factors for Tuberculin Positivity in Drug Users, Clinical Infectious Diseases, 35, pp. 1183-1190, 2002.

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

Research Findings - Epidemiology and Etiology Research

Monitoring the Future Study

The results from the 2002 annual Monitoring the Future (MTF) survey of 8th, 10th, and 12th grade students in U.S. schools were released in December 2002. The findings indicate that use of marijuana, several other illicit drugs, cigarettes and alcohol decreased from 2001 to 2002. The percentages of 8th and 10th graders using any illicit drug declined and were at their lowest level since 1993 and 1995, respectively. Marijuana use decreased among 10th graders; LSD use was down among students in each grade; and MDMA (Ecstasy) use decreased in each grade, though declines were statistically significant only for 10th graders. Use of most other drugs, including cocaine and heroin, remained stable. No major drug use indicators increased. Cigarette smoking decreased in each grade, expanding on a recent trend. Alcohol use and having "been drunk" were down among 8th and 10th graders, and binge drinking decreased among 10th graders.

Attitudes toward substance use, often seen as harbingers of change in rates of use, were mostly stable, but both perceived risk of harm from using MDMA and disapproval of using this drug increased in each grade. Perceived availability of LSD was down in each grade, and perceived availability of alcohol and cigarettes decreased in grades 8 and 10.

Monitoring the Future, which is conducted by the University of Michigan under a grant from NIDA, has been tracking drug use among seniors for 28 years and among 8th and 10th graders since 1991. The 2002 sample consisted of around 43,700 students in 394 schools in the coterminous U.S.

The changes noted below are statistically significant unless otherwise indicated.

Marijuana

- Among 10th graders, marijuana/hashish use in the past year and past month decreased and daily use in the past month was down. Past year use decreased from 32.7 percent to 30.3 percent; past month use went from 19.8 percent to 17.8 percent, and daily use in the past month declined from 4.5 percent to 3.9 percent.
- For the 8th graders, there has been slow but steady progress toward reduction of marijuana use. The past year marijuana use rate for 8th graders in 2002 -- 14.6 percent -- is the lowest rate seen since 1994, and well below the recent peak of 18.3 percent in 1996.

Cocaine

- Cocaine use remained statistically unchanged from 2001 to 2002 for each grade and recency period. Past year cocaine use was reported by 2.3 percent of 8th graders, 4.0 percent of 10th graders, and 5.0 percent of 12th graders.
- This comes after declines in cocaine use among 10th graders from 2000 to 2001 and among 12th graders between 1999 and 2000.
- Crack use showed a significant increase in past year use among 10th graders, returning to around its 2000 level following a decline in 2001.

Heroin and Other Opiates

- Heroin use by 8th, 10th and 12th graders remained stable from 2001 to

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2002 following a decline from 2000 to 2001 among 10th and 12th graders. Past year use rates were around 1 percent in each grade.

- New questions on nonmedical use of Oxycontin and Vicodin in the past year were added in the 2002 survey for each grade, and the findings give some reason for concern.
    - Oxycontin use in the past year without a doctor's orders was reported by 1.3 percent of 8th graders, 3.0 percent of 10th graders, and 4.0 percent of 12th graders.
    - Nonmedical use of Vicodin in the past year was reported by 2.5 percent of 8th graders, 6.9 percent of 10th graders, and 9.6 percent of 12th graders.

Inhalants

- Inhalant use in the lifetime decreased among 8th and 10th graders and past use decreased among 8th graders. Lifetime use went from 17.1 percent in 2001 to 15.2 percent in 2002 among 8th graders and from 15.2 percent to 13.5 percent among 10th graders.
- In 2002, inhalant use among 8th and 10th graders in all recency periods was the lowest seen in the history of the survey and the lowest in about 20 years for seniors.

Hallucinogens

- Hallucinogen use in the lifetime, past year, and past month declined for 12th graders, and past year use was down among 10th graders.
- LSD showed major changes from 2001 to 2002. Rates of use decreased markedly in each grade and recency period. Past year use, for example, declined from 6.6 percent to 3.5 percent among 12th graders, from 4.1 percent to 2.6 percent among 10th graders and from 2.2 percent to 1.5 percent among 8th graders. These are the lowest rates of LSD use in the history of the survey for each grade.

Club Drugs

- Rates of MDMA (Ecstasy) use decreased significantly among 10th graders. For this grade, past year use declined from 6.2 percent to 4.9 percent and past month use went from 2.6 percent to 1.8 percent. Use by 8th and 12th graders also showed signs of decline.

Use of Cigarettes and Smokeless Tobacco

- Cigarette use declined in each grade and several categories of use between 2001 and 2002.
    - Lifetime use - 8th grade - 36.6 percent to 31.4 percent; 10th grade - 52.8 percent to 47.4 percent; 12th grade - 61.0 percent to 57.2 percent.
    - Past month use - 8th grade - 12.2 percent to 10.7 percent; 10th grade - 21.3 percent to 17.7 percent; 12th grade - 29.5 percent to 26.7 percent.
    - Daily use in past month - 10th grade - 12.2 percent to 10.1 percent; 12th - 19.0 percent to 16.9 percent.
- This follows several years of gradual decreases in cigarette smoking that started around 1996 for 8th graders and 1997 for 10th and 12th graders. However, year-to -year declines have not always been statistically significant in all grades, and the decreases seen between 2001 and 2002 are particularly notable.
- Use of bidis in the past year declined among 10th graders from 4.9 percent in 2001 to 3.1 percent in 2002. Use of these small, flavored cigarettes from India was reported by 2.7 percent of 8th graders and 5.9 percent of 12th graders in 2002 based on the past-year reporting period. Use of Kreteks (clove-flavored cigarettes from Indonesia) in the past year was reported by 2.6 percent of 8th graders; 4.9 percent of 10th graders, and 8.4 percent of 12th graders in 2002.
- Lifetime use of smokeless tobacco by 10th graders declined from 19.5 percent in 2001 to 16.9 percent in 2002.

Alcohol Use

- Between 2001 and 2002 significant reductions in alcohol use were observed among 8th and 10th graders in numerous categories of use, including lifetime, past year, and past month. The use rates in 8th and 10th graders are record lows in the history of the survey in those grades.
- Rates of having been drunk in the lifetime and past year decreased for 8th and 10th graders. Among 10th graders, the rate of binge drinking (five or more drinks in a row) in the past two weeks declined, as did the past-month rate of having been drunk.

Perceived Harmfulness, Disapproval, and Perceived Availability

- Both perceived risk and disapproval of trying marijuana once or twice increased among 10th graders, but among 12th graders perceived risk of smoking marijuana regularly declined.
- Attitudes toward MDMA (Ecstasy) use hardened. Perceived risk of occasional MDMA use increased among 8th graders and perceived risk of trying it once or twice increased among 10th and 12th graders. Disapproval of MDMA use from 2001 to 2002 increased significantly among students in all three grades.
- Perceived risk and disapproval of trying LSD once or twice both increased among 12th graders, but among 10th graders perceived risk of regular LSD use decreased. Notably, perceived availability of LSD declined among students in all three grades.
- Perceived risk of trying inhalants once or twice declined among 8th graders, and perceived risk of regular use of these substances decreased among 10th graders. Seniors are not asked about their attitudes regarding inhalant use.
- Perceived availability of amphetamines decreased among 8th graders.

Substance Dependence, Antisocial Behavior, and Personality

The authors present a biometric model to explain patterns of comorbidity among substance dependence, antisocial behavior, and disinhibitory personality traits, which commonly co-occur. Hierarchical models were fit using data from the Minnesota Twin Family Study. Analyses indicated that a highly heritable externalizing factor accounts for much of the co-occurrence among alcohol dependence, drug dependence, conduct disorder, adolescent antisocial behavior, and disinhibitory personality style. However, variance within each syndrome suggests that both genetic and environmental factors contribute to these distinctions. These findings may help shape strategies for delineating the specific genes and environmental conditions that account for each of these conditions. Krueger, R.F., Hicks, B.M., Patrick C.J., Carlson, S.R., Iacono, W.G., and McGue, M. Etiologic Connections Among Substance Dependence, Antisocial Behavior, and Personality: Modeling the Externalizing Spectrum. Journal of Abnormal Psychology, 111, pp. 411-424, 2002.

Psychiatric Disorders and Substance Abuse Disorders Among Youth in Juvenile Detention

Data are from a large (1829 youth, ages 10-18), random sample of male and female, white, African-American and Hispanic juvenile detainees in Cook County, IL. Among teens in juvenile detention, nearly two thirds of boys and nearly three quarters of girls have at least one psychiatric disorder. These rates dwarf the estimated 15 percent of youth in the general population thought to have psychiatric illness. Even when conduct disorder (common in this population) was excluded, nearly 60 percent of males and more than two-thirds of females met diagnostic criteria for, and also were functionally impaired by, one or more mental or substance use disorder. Half of males and almost half of females had a substance use disorder. Overall, disorders were more prevalent among older youth and females, more than 20 percent of whom had a major depressive disorder. Among boys, non-Hispanic whites had the highest prevalence for most disorders and African Americans the lowest. The exception was separation anxiety disorder, which was more prevalent among African Americans and Hispanics than among whites. Hispanics had higher prevalence than African Americans for panic disorder, obsessive-compulsive disorder and substance use other than alcohol or marijuana disorders. The only categories for which boys had higher prevalence than girls were manic episode, psychotic disorders, any substance abuse disorder, and marijuana use disorder. Longitudinal data are currently being collected on these youth. Teplin, L.A., Abram, K.M., McClleland, G.M., Dulcan, M.K., and

Mericle, A.A. Psychiatric Disorders in Youth in Juvenile Detention. Arch. Gen. Psychiatry, 59, pp. 1133-1143, 2002.

Prevalence and Age of Onset for Drug Use in Seven International Sites

Kessler and colleagues present results of analyses of patterns of substance use utilizing data from seven population-based surveys carried out in six countries including the U.S., Canada, Brazil, Mexico, Germany and the Netherlands. All surveys utilized the Composite International Diagnostic Instrument (CIDI) to ascertain drug use. This study compares lifetime prevalence and age of first use for alcohol, cannabis, and other drugs. Alcohol and cannabis are the most widely consumed substances across all sites. Use of cannabis five or more times in a lifetime ranged from 28.8% in the U.S. to 1.7% in Mexico. While prevalence of use of different drugs varied widely from site to site, age of first use was similar across study sites. The authors suggest that this reflects a potentially strong linkage to stages of adolescent development and the influence of social role transitions in early adulthood. Comparisons of data from Mexico City, U.S., and Fresno, California (sample of Mexican-origin respondents including immigrants and U.S. born) revealed that lifetime drug use rates in the Fresno sample are lower than the national U.S. rates, but higher than those for the Mexico City population. The authors conclude that these findings suggest that drug use patterns may change among emigrating populations from low consumption nations as a consequence of international resettlement in nations with higher rates. Vega, W., Aguilar-Gaxiola, S., Andrade, L., Bijl, R., Borges, G., Caraveo-Anduaga, J., DeWit, D., Heeringa, S., Kessler, R.C., Kolody, B., Merikangas, K., Molnar, B., Walters, E., Warner, L., and Wittchen, H. Prevalence and Age of Onset for Drug Use in Seven International Sites: Results from the International Consortium of Psychiatric Epidemiology. Drug and Alcohol Dependence, 68, pp. 285-297, 2002.

The Gateway Hypothesis

Dr. Kandel has edited a book that represents the first systematic discussion of the "Gateway Hypothesis." The volume presents a critical overview of what is currently known about the hypothesis. The authors of the chapters explore the hypothesis from various perspectives ranging from developmental social psychology to prevention and intervention science, animal models, neurobiology, and analytical methodology. Kandel, D.B., Ed. Stages and Pathways of Drug Involvement: Examining the Gateway Hypothesis. Cambridge, UK: Cambridge University Press, 2002.

Genetic Effects of Antisocial Personality Disorder Associated With Major Depression, Alcohol Dependence, and Marijuana Dependence

This study examined the contribution of genetic effects associated with antisocial personality disorder (ASPD) to the comorbidity of major depression (MD), alcohol dependence (AD), and marijuana dependence (MD) using the Vietnam Era Twin Registry, a general population registry of male veteran twins. A telephone diagnostic interview for DSM-III-R disorders was administered in 1992 to 3360 pairs (1868 MZ and 1492 DZ). Structural equation modeling was performed to estimate additive genetic, shared environmental, and nonshared environmental effects common and specific to each disorder. The heritability estimates for lifetime ASPD, MD, AD, and MJD (marijuana dependence) were 69%, 40%, 56%, and 50%, respectively. Genetic effects on ASPD accounted for 38%, 50%, and 58% of the total genetic variance in risk for MD, AD, and MJD, respectively. After controlling for genetic effects on ASPD, the partial genetic correlations of MD with AD and with MJD were no longer statistically significant. Genetic effects specific to MD and AD and familial effects specific to MJD remained statistically significant. Nonshared environmental contributions to the comorbidity in these disorders were small. The findings indicate that the shared genetic risk between MD and both AD and MJD was largely explained by genetic effects on ASPD, which in turn was associated with increased risk of each of the other disorders. Fu, Q., Heath, A.C., Bucholz, K.K., Nelson, E., Goldberg, J., Lyons, M.J., True, W.R., Jacob, T., Tsuang, M.T., and Eisen, S.A. Archives of General Psychiatry, 59(12), pp.1125-1132, 2002.

Effectiveness of a Universal Drug Abuse Prevention Approach For Youth At High Risk For HOPA Polymorphism Associated With Major Depression, Phobia, and Antisocial Diathesis

This study examined the relationship between thyroid receptor co-activator named HOPA polymorphisms and neuropsychiatric illness in a cohort of Iowa adoptees. Consistent with prior findings, HOPA polymorphisms were associated with an increased risk for major depression and phobia. There was suggestive evidence of

gene-by-gene interactive effects (i.e., epistasis) in that the increased psychiatric morbidity was elevated in subjects with alcoholic or antisocial behavior in the biologic father. For example, 80% of females positive for HOPA variants, compared to 41% of females negative for HOPA variants, had this high-risk biologic background. In summary, HOPA polymorphisms may be a moderate risk factor for increased susceptibility to a broad spectrum of neuropsychiatric illness and that the type of illness manifested might be related to a separate genetic diathesis. Philibert, R., Caspers, K., Langbehn, D., Troughton, E.P., Yucuis, R., Sandhu, H.K., Cadoret, R.J. The Association of a HOPA Polymorphism with Major Depression and Phobia. Comprehensive Psychiatry, 43(5), pp. 404-410, 2002.

Prior Violence and Childhood Psychiatric History, But Not Substance Abuse, Predict Violence

The study examined whether scores on the Violence Proneness Scale, history of child and parent psychopathology, and substance abuse, could predict violence at age 19. At age 12-14, biological sons of fathers with and without substance use disorder completed a 13-item Violence Proneness Scale, which was derived by using items from the revised Drug Use Screening Inventory. The occurrence of violent acts was then assessed at a follow-up evaluation when the offspring were 19 years of age. A DSM-III-R axis I psychiatric disorder and a Violence Proneness Scale score of 10 or higher at age 12-14 predicted a violent outcome by age 19. The overall accuracy of prediction was 77%. Sensitivity was 81%, and specificity was 76%. Substance use disorder or psychopathology in the probands or substance use frequency in the children did not contribute to the prediction of violence. Tarter, R.E., Kirisci, L., Vanyukov, M., Cornelius, J., Pajer, K., Shoal, G.D., and Giancola, P.R. American Journal of Psychiatry, 159(9), pp. 1541-1547, 2002.

Poor Self-Control Associated With Escalation of Substance Use

This research tested predictions about the role of temperament and self-control in substance use (tobacco, alcohol, and marijuana) in a sample of 1,526 participants assessed in 6th grade (mean age = 11.5 years) and followed with yearly assessments through 9th grade. Latent growth curve modeling indicated that the rate of growth in substance use was higher among participants who showed increases in poor self-control and lower among participants who showed increases in good self-control. Wills, T.A. and Stoolmiller, M. Journal of Consulting and Clinical Psychology, 70(4), pp. 986-997, 2002.

Adolescent Substance Abuse and Psychiatric Comorbidity

As part of a special journal section on child psychopathology and drug abuse, the authors reviewed published studies using community samples and DSM or ICD classifications to assess rates, specificity, timing, and differential patterns of comorbidity by gender, race/ethnicity, and other factors. They found high rates of comorbidity in community samples; about 60% of youths with substance use, abuse, or dependence have a comorbid psychiatric disorder, with conduct disorder and oppositional defiant disorder the most common. Psychopathology was generally associated with earlier onset of substance use and with substance abuse. The nature of the data limited the authors' ability to explore risk factors, but they feel that current studies show promise for further work in this area. Armstrong, T.D. and Costello, E.J. Community Studies on Adolescent Substance Use, Abuse, or Dependence and Psychiatric Comorbidity. Journal of Consulting and Clinical Psychology, 70, pp. 1224-1239, 2002.

Child Neglect Associated With Increased Risk For Substance Abuse

This article critically reviews the empirical literature pertaining to the prevalence, origins, and consequences of neglectful parenting as it relates to substance abuse. Available evidence indicates that children who experience parental neglect, with or without parental alcohol or drug abuse, are at high risk for substance use disorder (SUD). The effects of parental substance abuse on substance abuse outcome of their children appear to be partly mediated by their neglectful parenting. The discussion concludes with presentation of a developmental multifactorial model in which neglect, in conjunction with other individual and environmental factors, can be integratively investigated to quantify the child's overall liability across successive stages of development as well as to map the trajectory toward good and poor outcomes. Dunn, M.G., Tarter, R.E., Mezzich, A.C., Vanyukov, M., Kirisci, L., and Kirillova, G. Clinical Psychology Review, 22(7), pp. 1063-1090, 2002.

Diminished Cortisol Response Among Offspring of Drug-Dependent Fathers

This report examines the salivary cortisol responses in preadolescent sons and daughters of fathers with and without drug-dependence, and the relative role of family environment. The high-risk boys and girls, relative to offspring of controls, demonstrated a diminished cortisol response in anticipation of a moderate stressor. Girls had significantly higher salivary cortisol concentrations, pre- and post-stressor. No association was found between salivary cortisol responses and measures of the family environment, however. These results suggest that there may be a sex difference in salivary cortisol dynamics in at-risk preadolescent children that is unrelated to current family environment. Hardie, T.L., Moss, H.B., Vanyukov, M.M., Yao, J.K., and Kirillovac, G.P. Psychiatry Research, 112(2), pp. 121-131, 2002.

Substance Use and Abuse By Asian Americans and Pacific Islanders From Four National Epidemiologic Studies

This report analyzed four recent large national surveys to assess the degree of use and abuse of a wide range of psychoactive substances across subgroups of Asian Americans and Pacific Islanders (AAPIs) and in comparison with whites. The surveys analyzed were the 1999 National Household Survey on Drug Abuse, the 1992 National Longitudinal Alcohol Epidemiologic Survey, and the 1995 National Longitudinal Study of Adolescent Health In-School and In-Home surveys. The AAPI sample sizes varied from 900 to more than 4,500 across the four surveys. Results showed that the rates of substance use are lowest for AAPIs. Mixed-heritage AAPIs are at high risk for substance use, with Japanese Americans having the highest substance use rates. Differential rates correspond to the ranking of several acculturation and socioeconomic indices. Results highlight the heterogeneity among AAPIs and point to the importance of studying socioenvironmental and potentially genetic protective factors associated with substance use in mixed-heritage adolescents. Price, R.K., Risk, N.K., Wong, M.M., and Klingle, R.S. Public Health Reports, 117(Suppl 1), pp. S39-S50, 2002.

Long-Term Psychological Sequelae of Smoking Cessation and Relapse

This study examined whether smoking cessation and relapse were associated with changes in stress, negative affect, and smoking-related beliefs. Quitters showed decreasing stress, increasing negative health beliefs about smoking, and decreasing beliefs in psychological benefits of smoking. Quitters became indistinguishable from stable nonsmokers in stress and personalized health beliefs, but quitters maintained stronger beliefs in the psychological benefits of smoking than stable nonsmokers. Relapse was not associated with increases in stress or negative affect. However, relapsers increased their positive beliefs about smoking and became indistinguishable from smokers in their beliefs. Findings suggest that decreased stress and negative beliefs about smoking may help quitters maintain successful cessation, but that declining health risk perceptions may undermine future quit attempts for relapsers. Chassin, L., Presson, C.C., Sherman, S.J., and Kim, K. Health Psychology, 21(5), pp. 438-443, 2002.

Parental Smoking Cessation May Help Decrease Adolescent Smoking

This study examined the relation of parent smoking cessation and adolescent smoking behavior. Participants were 446 adolescents and their parents who completed a computerized measure of implicit attitudes toward smoking and questionnaires assessing smoking, parenting, and explicit attitudes. Parental smoking cessation was associated with less adolescent smoking, except when the other parent currently smoked. Children's reports of parents' antismoking behavior partially mediated the relation between parental smoking and adolescent smoking. Although children's implicit and explicit attitudes were unrelated to parental smoking, mothers' implicit attitudes were related to both their own smoking and their child's smoking. Findings suggest that parental smoking cessation may help lower risk for adolescent smoking - but only if the other parent does not currently smoke. Chassin, L., Presson, C., Rose, J., Sherman, S.J., and Prost, J. Journal of Pediatric Psychology, 27(6), pp. 485-496, 2002.

Child Maltreatment and Adulthood Violence: The Contribution of Attachment and Drug Abuse

This study examined the association between child maltreatment and adult violence in a high-risk sample of women with and without a history of cocaine abuse and the contribution of working models of childhood attachment relationships in understanding this association. Results indicated that whereas childhood physical abuse was associated with adult sexual victimization for cocaine-abusing women, sexual abuse was associated with both partner violence victimization and perpetration

for comparison women. Insecure working models of attachment were associated with partner violence victimization for comparison women, independent of the effect of sexual abuse. These findings suggest the importance of research focused on understanding the processes by which child maltreatment may lead to later violence and that examines both childhood and adulthood experiences in understanding pathways to adult violence. Feerick, M.M., Haugaard, J.J., and Hien, D.A. Child Maltreatment, 7(3), pp. 226-240, 2002.

Exploring Why Drug Abuse Epidemics Occur in Different Groups at Different Times: Case Study of Heroin Use Among African Americans in Baltimore City in the 1960s

Agar utilized a broad array of data sources including ethnographic data from drug users, media archives, historical accounts, professional literature from the 1960s and autobiographies to analyze the increase in heroin use and addiction among African Americans in Baltimore City, Maryland, in the 1960s. This study is part of a broader project to develop a theory to explain drug abuse trends with particular temporal and spatial contexts. Agar's approach is to integrate political, socioeconomic and cultural factors within a historical framework and to illustrate the dynamic interaction of factors operating at multiple levels. The authors conclude that a drug abuse "trend" emerges at the convergence of three types of events: (1) rapid change in the distribution and marketing systems, (2) rapid movement of a population into a situation of open marginality and the acute despair that follows, and (3) the forging (or strengthening) of social links between distributors and consumers. With respect to the Baltimore 1960s context, the investigators found that the two most important historical processes behind the 1960s epidemic were the changing distribution/supply system at international and local levels, and the mix of hope and despair that was part of the civil rights movement that impacted the African American community in Baltimore. Agar, M. and Reisinger, H.S. A Heroin Epidemic at the Intersection of Histories: The 1960s Epidemic Among African Americans in Baltimore. Medical Anthropology, 21, pp. 115-156, 2002.

Overview of Measuring Risks and Outcomes in Drug Abuse Research

This paper describes principles and procedures for developing a comprehensive assessment of childhood risk factors and substance abuse outcomes. A conceptual framework is provided, procedures for identifying relevant measurement domains are described, steps necessary in creating an assessment protocol are outlined, selected instruments are described as examples, and resources available for more comprehensively identifying available measures are described. The risks specifically reviewed in this article include family history, childhood maltreatment, peer relationships, and psychopathology. The substance use measures reviewed include substance type, consumption quantity and frequency and substance related problems. Clark, D.B., and Winters, K.C. Measuring Risks and Outcomes in Substance Use Disorders Prevention Research. J of Consulting and Clinical Psychology, 70(6), pp. 1207-1233, 2002.

Correlates of Marijuana Use in Colombian Adolescents: A Focus on the Impact of the Ecological/Cultural Domain

This study examined the influence of ecological/cultural factors and family, personality, and peer factors present during early adolescence that influence marijuana use in late adolescence. A community sample of 2,226 Colombian adolescents living in mixed urban-rural communities and their mothers were interviewed in their homes by trained Colombian interviewers, first in 1995-1996 and then again two years later. The scales used were based on item intercorrelations and grouped into the following categories: (1) adolescent personality, (2) family traits, (3) peer factors, (4) ecological/ cultural variables, and (5) marijuana use. Data were examined using hierarchical regression modeling to determine the relationship between each of the domains and late adolescent marijuana use. The findings supported the family interactional theory of adolescent drug use behavior and found that factors in all of the domains had both a direct effect on late adolescent marijuana use as well as indirect effects mediated through the more proximal domains in the model. Of particular interest was the strength of the influence of the ecological/cultural factors, which far exceeded that observed in similar studies done in the United States. Due to the similarity with findings from studies conducted in the U.S., interventions designed domestically could effectively be directly applied to adolescents in Colombia. The findings also suggest that prevention programs designed specifically to target ecological or cultural factors may have the most profound influence for reducing marijuana use in late adolescence. Brook, D.W., Brook J.S. and Rosen, Z. Correlates of Marijuana Use in Colombian Adolescents: A

Focus on the Impact of the Ecological/Cultural Domain. Journal of Adolescent Health, 31, pp. 286-298, 2002.

Early Adolescent Marijuana Use: Risks for the Transition to Young Adulthood

This study assessed the relationship of early adolescent marijuana use to performance of developmental tasks integral to the transition to young adulthood. The tasks concerned intimacy, education, and work and social conformity. African American (N=617) and Puerto Rican (N=531) youths completed questionnaires in their classrooms. Five years later they were individually interviewed. Logistic regression analysis estimated the increased likelihood that early marijuana users would make an inadequate transition to young adult social roles. Analyses examining the association between early marijuana use and twenty outcome variables found significant relationships for ten of them: (a) having lower educational and occupational expectations; (b) being suspended or expelled from school, fired from jobs, 'high' at school or work, collecting welfare; and (c) rebelliousness, not participating in productive activities, not attending church, and being an unmarried parent. Marijuana use was not related to any of the intimate relationship measures. These finding emerged with controls on gender, ethnicity, age, and mother's education. Among African Americans and Puerto Ricans, early marijuana use predicts less adequate performance on some developmental tasks integral to becoming an independent young adult. Marijuana is not a benign drug and is associated with future risks for the individual and society at large. Brook, J.S., Adams, R.E., Balka, E.B. and Johnson, E. Early Adolescent Marijuana Use: Risks for the Transition to Young Adulthood. Psychological Medicine, 32, pp. 79-91, 2002.

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

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

Childhood Adversities Associated With Risk for Eating Disorders or Weight Problems During Adolescence or Early Adulthood

A community-based prospective longitudinal study was conducted to investigate the association between childhood adversities and problems with eating or weight during adolescence and early adulthood. A sample of 782 mothers and their offspring were interviewed during the childhood, adolescence, and early adulthood of the offspring. Childhood maltreatment, eating problems, environmental risk factors, temperament, maladaptive parental behaviors and parental psychopathology were assessed during childhood and adolescence. Eating disorders and problems with eating or weight in the offspring were assessed during adolescence and early adulthood. A wide range of childhood adversities were associated with elevated risk for eating disorders and problems with eating or weight during adolescence and early adulthood after the effects of age, childhood eating problems, difficult childhood temperament, parental psychopathology, and co-occurring childhood adversities were controlled statistically. Numerous unique associations were found between specific childhood adversities and specific types of problems with eating or weight, and different patterns of association were obtained among the male and female subjects. Maladaptive paternal behavior was uniquely associated with risk for eating disorders in offspring after the effects of maladaptive maternal behavior, childhood maltreatment, and other co-occurring childhood adversities were controlled statistically. Childhood adversities may

contribute to greater risk for the development of eating disorders and problems with eating and weight that persist into early adulthood. Maladaptive paternal behavior may play a particularly important role in the development of eating disorders in offspring. Johnson, J.G., Cohen, P., Kasen, S. and Brook, J.S. Childhood Adversities Associated With Risk for Eating Disorders or Weight Problems During Adolescence or Early Adulthood. American Journal of Psychiatry. 159, pp. 394-400, 2002.

Drug Use and Neurobehavioral, Respiratory, and Cognitive Problems: Precursors and Mediators

To test a model of the early predictors and mediators of drug use and respiratory, neurobehavioral, and cognitive problems in adolescence and young adulthood. Authors prospectively examined self-reported measures of unconventional behavior, peer- and self-drug use and self-reported health problems in a sample of 286 males and 327 females. The sample represented the Northeastern United States at the time the data was first collected in 1975. The participants were assessed in early, middle, and late adolescence, and in young adulthood. Latent variable structural equation models were used to examine the data. Structural equation modeling conducted on the data provided support for the proposed longitudinal model. The findings indicated that adolescent drug use was associated indirectly with respiratory and directly with neurobehavioral and cognitive symptoms in young adulthood. Adolescent drug use during middle and late adolescence served as a mediator between unconventional behavior in early adolescence and health problems in young adulthood. A reduction in adolescent drug use may reduce respiratory and neurobehavioral and cognitive symptoms in young adulthood. This study identifies several points in the biopsychosocial pathways in adolescence leading to later health problems in young adulthood. Brook, J.S., Finch S.J., Whiteman, M. and Brook, D.W. Drug Use and Neurobehavioral, Respiratory, and Cognitive Problems: Precursors and Mediators. Journal of Adolescent Health, 30, pp. 433-441, 2002.

Eating Disorders During Adolescence and the Risk for Physical and Mental Disorders During Early Adulthood

Data from a community-based longitudinal investigation were used to investigate whether adolescents with eating disorders are at an elevated risk for physical and mental disorders during early adulthood. Psychosocial and psychiatric interviews were administered to a representative community sample of 717 adolescents and their mothers from 2 counties in the state of New York in 1983, 1985 to 1986, and 1991 to 1993. In 1983, the mean age of the youths was 13.8 years. Adolescents with eating disorders were at a substantially elevated risk for anxiety disorders, cardiovascular symptoms, chronic fatigue, chronic pain, depressive disorders, limitations in activities due to poor health, infectious diseases, insomnia, neurological symptoms, and suicide attempts during early adulthood after age, sex, socioeconomic status, co-occurring psychiatric disorders, adolescent health problems, body mass index, and worries about health during adulthood were controlled statistically. Problems with eating or weight during adolescence predicted poor health outcomes during adulthood, regardless of whether an eating disorder had been present. Only 22% of the adolescents with current eating disorders had received psychiatric treatment within the past year. Eating disorders during adolescence may be associated with an elevated risk for a broad range of physical and mental health problems during early adulthood. Johnson, J.G., Cohen, P., Kasen, S. and Brook J.S. Eating Disorders During Adolescence and the Risk for Physical and Mental Disorders During Early Adulthood. Archives of General Psychiatry, 59, pp. 545-552, 2002.

Television Viewing and Aggressive Behavior During Adolescence and Adulthood

Television viewing and aggressive behavior were assessed over a 17-year interval in a community sample of 707 individuals. There was a significant association between the amount of time spent watching television during adolescence and early adulthood and the likelihood of subsequent aggressive acts against others. This association remained significant after previous aggressive behavior, childhood neglect, family income, neighborhood violence, parental education, and psychiatric disorders were controlled statistically. Johnson, J.G, Cohen, P., Smailes, E.M., Kasen, S. and Brook, J.S. Television Viewing and Aggressive Behavior During Adolescence and Adulthood. Science, 295, pp. 2468-2471, 2002.

Psychiatric Disorders Associated with Risk for the Development of Eating Disorders During Adolescence and Early Adulthood

Longitudinal data were used to investigate whether anxiety, depressive, disruptive,

personality, or substance use disorders are associated with risk for the development of eating disorders during adolescence or early adulthood. Psychiatric disorders were assessed among 726 youths from a random community sample during adolescence and early adulthood. Depressive disorders during early adolescence were associated with elevated risk for the onset of eating disorders, dietary restriction, purging behavior, and recurrent weight fluctuations after preexisting eating problems and other psychiatric disorders were controlled statistically. Disruptive and personality disorders were independently associated with elevated risk for specific eating or weight problems. The present findings suggest that depressive disorders during early adolescence may contribute to the development of eating disorders during middle adolescence or early adulthood. Johnson, J.G., Cohen, P., Kotler, L., Kasen, S. and Brook J.S. Psychiatric Disorders Associated with Risk for the Development of Eating Disorders During Adolescence and Early Adulthood. Journal of Consulting and Clinical Psychology, 70 (5), pp. 1119-1128, 2002.

Childhood Adversities, Interpersonal Difficulties, and Risk for Suicide Attempts During Late Adolescence and Early Adulthood

Data from a community-based longitudinal study were used to investigate the association between childhood adversities, interpersonal difficulties during adolescence, and suicide attempts during late adolescence or early adulthood. A community sample of 659 families from Upstate New York was interviewed in 1975, 1983, 1985 to 1986, and 1991 to 1993. During the 1991-1993 interview, the mean age of the offspring was 22 years. Maladaptive parenting and childhood maltreatment were associated with an elevated risk for interpersonal difficulties during middle adolescence and for suicide attempts during late adolescence or early adulthood after age, sex, psychiatric symptoms during childhood and early adolescence, and parental psychiatric symptoms were controlled statistically. A wide range of interpersonal difficulties during middle adolescence were associated with risk for suicidal behavior after the covariates were controlled. Profound interpersonal difficulties during middle adolescence mediated the association between maladaptive parenting or childhood maltreatment and suicide attempts during late adolescence or early adulthood. Maladaptive parenting and childhood maltreatment may be associated with a risk for severe interpersonal difficulties during adolescence. These interpersonal difficulties may play a pivotal role in the development of suicidal behavior. Youths who are at an elevated risk for suicide may tend to be in need of mental health services that can help them to cope with an extensive history of profound interpersonal difficulties, beginning in childhood and continuing through adolescence. Johnson, J.G., Cohen, P., Gould, M.S., Kasen, S., Brown, J. and Brook, J.S. Childhood Adversities, Interpersonal Difficulties, and Risk for Suicide Attempts During Late Adolescence and Early Adulthood. Archives of General Psychiatry, 59, pp. 741-749, 2002.

Adolescent Life Events as Predictors of Adult Depression

Among adults, life events predict future episodes of major depression as well as a range of anxiety disorders. While studies have begun to examine this issue in adolescents, few studies rely upon prospective epidemiological designs to document relationships between adolescent life events and adult major depression. An epidemiologically-selected sample of 776 young people living in Upstate New York received DSM-based psychiatric assessments and an assessment of life events in 1986. Psychopathology was again assessed in 1992. The current study examined the predictive relationship between life events in 1986 and depression as well as anxiety in 1992, controlling for depression/anxiety in 1986. Adolescent life events predicted an increased risk for major depression diagnosis in adulthood. When analyzed continuously, an association emerged with symptoms of major depression as well as with symptoms of generalized anxiety disorder. However, this association with generalized anxiety disorder was limited to females. Life events in adolescence predict risk for major depression during early adulthood. Pine, D.S., Cohen, P., Johnson, J.G. and Brook, J.S. Adolescent Life Events as Predictors of Adult Depression. Journal of Affective Disorders, 68, pp. 49-57, 2002.

The Longitudinal Relationship Between Drug Use and Risky Sexual Behaviors Among Colombian Adolescents

Community samples representing differing levels of risky sexual behavior and drug use were use to identify the longitudinal relationships between drug use, and risky sexual behaviors and early pregnancy in Colombian adolescents . Cohorts were drawn from higher and lower risk geographic areas as well as from various self-reported ethnic groups. Using regression analyses, controlling for demographic variables, a reciprocal, longitudinal relationship between risky sexual behaviors and drug use was identified. Those adolescents who reported higher levels of drug use at T1 also had

more sexual partners and higher frequencies of unprotected sex, and they were also more likely to have experienced early pregnancy at T2. The reverse relationship was true as well. The level of violence experienced by the adolescent emerged as a moderator of some of these relationships. The results suggest that reducing adolescent drug use may also reduce levels of risky sexual behavior and early pregnancy and vice versa. Further, the importance of addressing violence as a risk factor for both problem behaviors is emphasized. Brook, D.W., Brook, J.S., Pahl, T. and Montoya, I., The Longitudinal Relationship Between Drug Use and Risky Sexual Behaviors Among Colombian Adolescents, Archives of Pediatric and Adolescent Medicine, 156, pp. 1101-1107, 2002.

Adolescent Children of Alcoholics Experience Difficulty With the Leaving-Home Transition

The current study examined the extent to which various features of young adults' experiences of leaving home differed for children of alcoholic (COAs) versus nonalcoholic parents. A total of 227 young adults drawn from a high-risk, community sample of COAs and matched controls were interviewed at ages 18-23 years regarding their prior leaving home experiences. COAs showed greater difficulties in negotiating this transition, fewer positive feelings about the transition, and different reasons for leaving home as compared to participants without an alcoholic parent. Moreover, adolescent risk behaviors, family conflict, and family disorganization (assessed prior to this transition) each partly accounted for COAs' risk for difficulty in the leaving home transition. Hussong, A.M. and Chassin, L. Developmental Psychopathology, 14(1), pp. 139-157, 2002.

Children of Opioid- and Alcohol-Dependent Parents

The authors compared families with parental opioid dependence, parental alcohol dependence, and no substance use disorder on several standardized measures. Children of opioid- and alcohol-dependent parents were found to have significantly higher rates of psychopathology, and difficulties in academic, social and family functioning, with problems of the offspring of opioid-dependent parents exceeding those of the alcohol-dependent. Children of opioid dependent parents showed more of a tendency toward disruptive, depressive, and anxiety disorders, while the alcohol group showed more depressive and substance use disorders, compared with controls. Differences in socioeconomic status and family intactness account for some of the group differences; nonetheless, the authors report that these findings are consistent with other literature on high-risk offspring. Wilens, T.E., Biederman, J., Bredin, E., Hahesy, A.L., Abrantes, A., Neft, D., Millstein, R., and Spencer, T.J. A Family Study of High-risk Children of Opioid- and Alcohol-dependent Parents. American Journal of Addictions, 11, pp. 41-51, 2002.

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

Research Findings - Prevention Research

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

The National Youth Anti-Drug Media Campaign (NYAMC) 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) determine if such change can be attributed to the Campaign. The findings summarized below are from the fifth 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 and 5th waves together include the first (of two) follow-up interviews of the initial samples. The new report covers the period from September 1999 through June 2002 and examines 1) exposure of youth and their parents to anti-drug messages (general exposure and specific exposure to ads run in the 2 months prior to the interview that are played on a computer to respondents); 2) effects on parents in terms of beliefs and behaviors associated with talking about drugs, and beliefs and behaviors regarding monitoring their child, and doing fun activities with their child; and 3) effects on youth cognitions, intentions, and initiation of drug use.

- **Exposure to and Recall of Campaign Messages**
  As in the 4th Report, most parents and youth recalled being exposed to NYAMC 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 the first three 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 and 50 percent during the first half of 2002. The current report indicates that both parents and youth reported substantial recognition of the Campaign's "anti-drug" brand phrases. The Campaign added Drugs and Terror ads targeted to both parents and youth during this period. The evaluation of these ads by both groups was somewhat less positive than the evaluation of the other ads broadcast during Wave 5.
- **Effects on Parents**
  There continues to be evidence suggesting a favorable Campaign effect on parents. Overall, there are favorable changes in 3 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 at time 1 measurement, were more likely subsequently to talk with their children and do fun activities with them. However, there is little evidence for Campaign effects on parents' monitoring behavior, the focus of the parent Campaign in the past year and the parent behavior most associated with youth nonuse of marijuana. Likewise, there is no evidence of favorable indirect effects on youth behavior as the result of parent exposure to the Campaign.
- **Effects on Youth**
  There is no evidence of direct favorable Campaign effects on youth.

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There is no statistically significant decline in marijuana use to date, and some evidence for an increase in use from 2000 to 2001. Nor are there improvements in anti-use beliefs and attitudes about marijuana between 2000 and the first half of 2002. Conversely, there are some unfavorable trends in youth anti-marijuana beliefs. In addition, there is no tendency for those reporting more exposure to Campaign messages to hold more desirable beliefs.

There continues to be evidence for an unfavorable delayed effect of Campaign exposure from September 1999 through June 2001 on subsequent intentions to use marijuana and on other beliefs and these are found for the entire sample. Whereas intentions are strong predictors of subsequent initiation of marijuana use, the evidence for an unfavorable effect on actual initiation was not statistically significant overall or for any subgroup. Thus, the behavioral evidence for some youth subgroups at Wave 4 was not confirmed once the entire sample was considered.

The full evaluation will involve three interviews with respondents over 3 1/2 years.

Effectiveness of a Universal Drug Abuse Prevention Approach For Youth At High Risk For Substance Use Initiation

Griffin and his colleagues examined the impact of universal school-based prevention programs for alcohol, tobacco, and other drug use for youth at high risk for substance use initiation. The effectiveness of a universal drug abuse preventive intervention was examined among youth from 29 inner-city middle schools participating in a randomized, controlled prevention trial. A subsample of youth (21% of full sample) was identified as at high risk for substance use initiation based on exposure to substance-using peers and poor academic performance in school. The prevention program taught drug refusal skills, anti-drug norms, personal self-management skills and general social skills. Findings indicated that youth at high risk who received the program (n = 426) reported less smoking, drinking, inhalant use, and polydrug use at the one-year follow-up assessment compared to youth at high risk in the control condition that did not receive the intervention (n = 332). Results indicate that a universal drug abuse prevention program is effective for minority, economically disadvantaged, inner-city youth who are at higher than average risk for substance use initiation. The findings from this study suggest that universal prevention programs can be effective for a range of youth along a continuum of risk. Griffin, K.W., Botvin, G.J., Nichols, T.R., and Doyle, M.M. Preventive Medicine, 36, pp. 1-7, 2003

Effective Family Intervention Embedded into the Public School Setting

The Adolescent Transitions Program (ATP) promotes student adjustment and reduces risk through a tiered intervention, involving universal, selective, and indicated intervention. The universal intervention places a family resource center in the schools for parenting resources and information supportive of protective parenting practices. The indicated intervention, a motivational interviewing process referred to as the Family Check Up, engages parents in appropriate family centered interventions. The indicated intervention involves a menu of options designed to strengthen effective family management practices. In this trial, 672 multiethnic students and their families were randomly assigned from the entire population of 6th grade students in three middle schools to the ATP intervention or to control. By the 9th grade, youth in the ATP program had a reduced incidence of a composite measure of tobacco or alcohol use compared to youth in the control group. The intervention effect did not differ by risk status or ethnicity. This study provides a successful model for embedding family interventions within the public school ecology. Dishion, T.J., Kavanagh, K., Schneiger, A., Nelson, S., and Kaufman, N. Preventing Early Adolescent Substance Use: A Family Centered Strategy for the Public Middle School. Prevention Science, 3(3), pp. 191-201, 2002.

Personal Competence Skills, Distress, and Well-Being As Determinants of Substance Use In A Predominantly Minority Urban Adolescent Sample

Several previous studies have investigated the relationship between psychological distress and substance use among youth. However, less research has investigated the potentially protective role of psychological well-being on adolescent substance use, and the extent to which personal competence skills may promote well-being. The present study examined personal competence skills, psychological distress and well-

being, and adolescent substance use over a three-year period in a predominantly minority sample of urban students (N = 1,184) attending 13 junior high schools in New York City. Structural equation modeling indicated that greater competence skills predicted less distress and greater well-being over time. While psychological well-being was associated with less subsequent substance use, distress did not predict later substance use. Findings indicate that competence skills promote resilience against early stage substance use in part by enhancing psychological well-being, and suggest that school-based prevention programs should include competence enhancement components in order to promote resilience. Griffin, K.W., Botvin, G.J., Scheier, L.M., Epstein, J.A., and Diaz, T. Prevention Science, 3, pp. 23-33, 2002.

Factors Associated With Regular Marijuana Use Among High School Students: A Long-Term Follow-Up Study

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

Life Skills Training As a Primary Prevention Approach for Adolescent Drug Use and Other Problem Behaviors

Alcohol, tobacco, and other drug use are important problems that typically begin during adolescence. Fortunately, substantial progress has been made in developing effective drug abuse prevention programs for youth over the past two decades. Prevention approaches that focus on the risk and protective factors associated with drug use initiation and those that teach skills related to social resistance are most effective. The Life Skills Training (LST) program is an effective primary prevention program for adolescent drug abuse that focuses on these factors as well as enhancing social and personal competence skills. This paper provides an overview of the theoretical underpinnings of the LST program, along with a description of the program's components, materials, and methods. Findings from over two decades of evaluation research are reviewed and demonstrate that the LST approach consistently produces positive behavioral effects on alcohol, tobacco, and other drug use. The role of competence enhancement-based primary prevention programs in preventing other negative behaviors during adolescence is discussed. Botvin, G.J., and and Griffin, K.W. International Journal of Emergency Mental Health, 4, pp. 41-47, 2002.

Positive Impact of Competence Skills and Psychological Wellness In Protecting Inner-City Adolescents From Alcohol Use

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

Estimates of Intragroup Dependence for Drug Abuse and Skills Measures Encountered In School-Based Drug Abuse Prevention Trials: An Empirical

Study of Three Independent Samples

Group-randomized drug abuse prevention trials customarily designate schools as the unit of assignment to experimental condition; however, students within schools remain the unit of observation. Students nested within schools may show some resemblance based on common (peer) selection or school climate factors (i.e., disciplinary practices, group norms, or rules). Appropriate analyses of any treatment effects must be statistically correct for the magnitude of clustering within these intact social units (i.e., intraclass correlation coefficient [ICC]). There is little reported evidence, however, of variation in ICCs that might occur with studies of racially or geographically diverse populations. The purpose of this study was to generate estimates of intragroup dependence for drug use and psychosocial measures (hypothesized mediators) from three separate drug abuse prevention trials. Clustering for the drug use measures averaged .02 across study and age-groups (range = .002 to .053) and was equivalently small for the psychosocial measures (averaging .03 across studies and age-groups; range = .001 to .149). With few exceptions and across different samples clustering decreased in magnitude over time. Clustering was largest for peer smoking and drinking norms among white, suburban youth and smallest for alcohol expectancies among urban black youth. Findings are discussed with respect to the influence of social climate factors and group norms in the design and analysis of school-based, drug abuse, prevention programs. Scheier, L.M., Griffin, K.W., Doyle, M.M., and Botvin, G.J. Health Education & Behavior, 29, pp. 85-103, 2002.

Culturally Sensitive Adaptation of Prevention Intervention

Very few family interventions have been adapted to be culturally sensitive for specific ethnic groups. This paper examines recruitment/retention and outcome effectiveness in five studies comparing standard and culturally adapted versions of the Strengthening Families Program (SFP). This selective prevention program is a 14-session family skills intervention involving parent, child, and family skills training components. Standard and adapted interventions were compared for African American, Hawaiian, Hispanic, and Native American families. Standard versions of the intervention tended to have slightly better outcomes, but recruitment and retention of families was 41% improved when implementing culturally adapted versions. Kumpfer, K.L., Alvarado, R., Smith, P., and Bellamy, N. Cultural Sensitivity and Adaptation in Family Based Prevention Interventions. Prevention Science, 3(3), pp. 241-246, 2002.

Friendships and Substance Use: Bi-directional Influence

The reciprocal relationship between deviant friendships and substance use was examined from early adolescence to young adulthood. Deviance within friendships was studied using direct observations of videotaped friendship interaction and global reports of deviant interactions with friends as well as time spent with friends. Substance use was assessed through youth self-report at all time points. Multivariate modeling revealed that substance use in young adulthood is a joint outcome of friendship influence and selection processes. In addition, substance use appears to influence the selection of friends in late adolescence. Findings suggest that effective prevention should target peer ecologies conducive to substance use and that treatment should address both the interpersonal underpinnings and addiction processes intrinsic to chronic use, dependence, and abuse. Dishion, T.J. and Owen, L.D. A Longitudinal Analysis of Friendships and Substance Use: Bi-directional Influence from Adolescence to Adulthood. Developmental Psychology, 38(4), pp. 480-491, 2002.

Sibling Collusion and Problem Behavior

Sibling collusion is a process whereby siblings form coalitions that promote deviance and undermine parenting. Collusive sibling processes were identified and measured using macro ratings of videotaped family interactions. Using a multiethnic urban 6th grade sample, investigators examined multiple questions, including whether more sibling collusion occurs in families with a high-risk child that with a normative child and whether sibling collusion can predict problem behavior. High-risk youth were identified by a smoking measure and a 16-item teacher rating of risk. High-risk youth who participated in a family assessment and had a sibling aged 10 or older (n=26) were matched with a normative target child on age, gender, ethnicity, and parental marital status (n=26). Siblings in families with a high-risk target child showed reliably higher rates of collusion than those in families with a normative target child. Sibling collusion also accounted for variance in problem behavior after controlling for involvement with deviant peers. Findings suggest that deviant conduct forms a common ground among siblings, potentially amplifying risk of mutuality in problem

behavior during early adolescence. Attention to sibling relationship processes is relevant to family interventions to prevent behavior problems. Bullock, B.M. and Dishion, T.J. Sibling Collusion and Problem Behavior in Early Adolescence: Toward a Process Model for Family Mutuality. Journal of Abnormal Child Psychology, 30(2), pp. 143-153, 2002.

Combining School-based and Family-based Intervention

This study evaluated the substance initiation effects of an intervention combining two empirically supported prevention interventions, one that is family-based and another that is school-based. Strengthening Families Program for Parents and Children 10-14 (SFP 10-14) is a family-based program designed to enhance parental skills in nurturing, limit setting, and communication as well as youth prosocial and peer resistance skills. Life Skills Training Program (LST) is a classroom-based prevention intervention designed to promote skill development in youth for the prevention of substance abuse. Thirty-six rural schools were randomly assigned to one of three conditions: 1) LST and SFP 10-14, 2) LST only, or 3) a control condition. Outcomes were examined one year after the intervention posttest, using a substance initiation index measuring lifetime use of alcohol, cigarettes, and marijuana and rates of use for individual substances. Both the combined and the LST interventions differed significantly (and favorably) from the control condition with regard to the substance initiation index and marijuana use, while the difference between the combined and LST-only programs was not significant for these measures. However, the combined program significantly reduced rates of alcohol initiation as compared to both the LST-only and control groups. Preliminary results suggest that the family-focused component may be particularly important in preventing the initial transition to 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 16(2), pp. 129-134, 2002.

Implementation Quality and Proximal Intervention Outcomes

The authors describe the results of two longitudinal studies of competency training interventions that involved community-university collaboration to enhance implementation quality. In Study 1, 22 rural schools were randomly assigned to a family-focused intervention or a minimal contact control group. In Study 2, 36 rural schools were randomly assigned to a family-focused preventive intervention combined with a school-based intervention, the school-based intervention alone, or a minimal contact control group. In both studies, observers rated adherence to intervention protocols. Results showed that, on average, high levels of observer-rated adherence were attained in both studies. Analyses of the relationship between observer-rated adherence scores and proximal outcomes showed limited evidence of poorer outcomes associated with lower adherence. Spoth, R., Guyll, M., Trudeau, L., and Goldberg-Lillehoj, C. Two Studies of Proximal Outcomes and Implementation Quality of Universal Preventive Interventions in a Community-University Collaboration Context. Journal of Community Psychology, 30(5), pp. 499-518, 2002.

Family Processes Predict Smoking Initiation

This study examined the relationship between family processes measured when children are in early elementary school and initiation of cigarette smoking in sixth or seventh grade in a sample of 810 suburban school children. Family process measures included both protective factors, such as attachment to parents and parent contact with school, and risk factors such as inconsistent discipline and family conflict. Measures of child attachment to parent and parent involvement with the child's school were significantly and negatively associated with smoking initiation when controlling for household structure and income, parent smoking, and peer and child characteristics. The results of these analyses suggest that enhancing the bonding process between parents and children and encouraging parents to be involved in the child's school may help prevent the initiation of smoking at the end of elementary school and the beginning of middle school. Fleming, C.B., Kim, H., Harachi, T.W., and Catalano, R.F. Family Processes for Children in Early Elementary School as Predictors of Smoking Initiation. Journal of Adolescent Health, 30, pp. 184-189, 2002.

Prevalence of Cigarette Smoking Among Rural Adolescents in the U.S.

Results are reported from a nationwide, U.S. study of cigarette smoking carried out from 1996 to 2000 involving 68,270 adolescents in grades 7 through 12 attending high school or the associated feeder junior high/middle school in a particular community. The sampling design was constructed to include students from a representative sample of rural communities in the United States. Based on responses

to cigarette use survey items, students were classified into one of eight user categories, ranging from being a non-user to being a heavy user (i.e., ongoing use of a half a pack or more per day). Hierarchical linear modeling was used to model smoking as a function of grade, gender, region, and community size (rurality). Significant effects were found for rurality, region, grade, and gender. The highest levels of smoking were found for rural adolescents and adolescents living in the South. Males smoked more than females in all regions except the West, where females smoked more. Given that rural adolescents smoke more "heavily" than do their nonrural peers, researchers should devote more attention to understanding the factors that underlie smoking initiation in rural youth. Aloise-Young, P.A., Wayman, J.C., and Edwards, R.W. Substance Use and Misuse, 37(5-7), pp. 613-630, 2002.

Explanations for Exposure Effects in an Anti-Drug Media Campaign

This study examines longitudinal evidence for the impact of exposure to an in-school media campaign on adolescent substance use attitudes and behaviors using data from four middle schools in two school districts. Amount of exposure to the campaign directly impacted perceptions that marijuana use was inconsistent with personal aspirations and intentions to use marijuana. It also was associated with a reduction in maturational decay in anti-drug attitudes. Path analyses suggested effects on behavior change, consistent with the Theory of Reasoned Action, occurred through their impact on intention, and exposure effects on intention, in turn, occurred by affecting aspirations. Reverse causation was tested and rejected, as were possible moderation models that might also qualify exposure effects. Analyses of a foil recognition measure using a treatment and control population suggested that response set artifacts were nominal in size, and that response bias was slight and could be statistically controlled. Slater, M.D. and Kelly, K. Testing Alternative Explanations for Exposure Effects in Media Campaigns: The Case of a Community-based, In-school Media Drug Prevention Project. Communication Research, 29, pp. 367-389, 2002.

Validating a Perceived Message Sensation Value (PMSV) Scale

Sensation seeking has been linked to drug abuse and risky behaviors, and with preferences for messages high in sensation value (i.e., perceived to be highly novel, arousing, dramatic, or intense). This suggests the value of developing a valid and reliable measure of perceived message sensation value (PMSV) for research on information processing, persuasion, and prevention. This article reports the dimensions and construct validity of a 17-item PMSV scale examined in 2 studies. In the first, 368 high school students' reactions to televised anti-marijuana public service announcements (PSAs) were explored; study 2 assessed 444 college students' responses to televised anti-cocaine PSAs. Exploratory and confirmatory factor analyses indicated 3-dimensional solutions for the PMSV scale were nearly identical for high sensation seeking (HSS) and low sensation seeking (LSS) respondents in Study 1 and HSS respondents in Study 2. Total scale alphas were .87 for Study 1 and .93 for Study 2. The PMSV scale and its three dimensions (i.e., Emotional Arousal, Dramatic Impact, Novelty) were positively correlated with affective response measures in both studies for HSS and LSS. Study 1 also examined cognitive, narrative, and sensory PSA processing. These were positively associated with total PMSV and the Arousal and Dramatic Impact dimensions of PSMV for both HSS and LSS. Palmgreen, P., Stephenson, M.T., Everett M.W., Baseheart J.R., and Francies R. Perceived Message Sensation Value (PMSV) and the Dimensions and Validation of a PMSV Scale. Health Communication 14(4), pp. 403-428, 2002.

Predictors of Exposure from an Anti-Marijuana Media Campaign

Using data from a large-scale anti-marijuana media campaign, this investigation examined the demographic and psychographic variables associated with exposure to public service announcements (PSAs) designed to target high sensation-seeking adolescents. The literature on sensation seeking indicates that adolescents high in this trait are at greater risk for substance abuse. This study assessed the predictive utility of various risk and protective factors, normative influences, demographic variables, and marijuana-related attitudes, intentions, and behaviors on campaign message exposure. The results confirm that the level of sensation seeking was positively associated with greater message exposure. In addition, viewers reporting greater exposure were younger adolescents who indicated that they had poor family relations, pro-marijuana attitudes, and friends and family who used marijuana. Implications for designing future anti-marijuana messages based on these findings are discussed. Stephenson M.T., Morgan S.E., Lorch E.P., Palmgreen P., Donohew L., and Hoyle R.H. Predictors of Exposure from an Anti-marijuana Media Campaign: Outcome Research Assessing Sensation Seeking Targeting. Health Communication,

14(1), pp. 23-43, 2002.

Drug-Moderating Effects of Peer Acceptance and Friendship on Family Adversity

Peer acceptance and friendships were examined as moderators in the link between family adversity and child externalizing behavioral problems. Data on family adversity (i.e., ecological disadvantage, violent marital conflict, and harsh discipline) and child temperament and social information processing were collected during home visits from 585 families with 5-year-old children. Socio-metric methods were used to assess children's peer acceptance, friendship, and friends' aggressiveness in kindergarten and grade one. Teachers rated children on externalizing behavior problems in grade two. Peer acceptance was a moderator for all three measures of family adversity, and friendship was a moderator for harsh discipline. Family adversity was not significantly associated with child externalizing behavior when levels of positive peer relationships were high. These moderating effects generally were not qualified by child gender, ethnicity, or friends' aggressiveness, nor were they accounted for by child temperament or social information-processing patterns. Criss, M.M., Pettit, G.S., Bates, J.E., Dodge, K.A., and Lapp, A.L. Family Adversity, Positive Peer Relationships, and Children's Externalizing Behavior: A Longitudinal Perspective on Risk and Resilience. Child Development, 73(4), pp. 1220-1237, 2002.

Behavioral Judgments and Aggression

Externalizing behavior problems of 124 adolescents were assessed in Grades 7-11. In Grade 9, participants' social-cognitive functioning was assessed following a task in which they imagined themselves to be the object of provocations portrayed in six videotaped vignettes. Participants responded to vignette-based questions representing response decision steps. Phase 1 of the investigation supported a two-factor model of the response decision (response valuation and outcome expectancy). Phase 2, after controlling for externalizing behavior in Grades 7-8, showed significant relations between the response decision processes, and response selection measured in Grade 9, and externalizing behavior in Grade 9, 10 and 11. These findings suggest that behavioral judgments about aggression play a crucial role in the maintenance and growth of aggressive response tendencies in adolescence. Fontaine, R., Salzer Burks, V., and Dodge, K.A. Response Decision Processes and Externalizing Behavior Problems in Adolescents. Development & Psychopathology, 14(1), pp. 107-122, 2002.

Social Information Processing and Aggressive Behavior

Social information processing (SIP) patterns were conceptualized in domains of process and context and measured through responses to hypothetical vignettes in a stratified sample of 387 children (50% boys; 49% minority) from 4 geographical sites followed from kindergarten through 3rd grade. Findings indicated that SIP constructs significantly predicted children's aggressive behavior problems as measured by later teacher reports. The findings support the construct validity of children's social cognitive patterns and the relevance of SIP patterns in children's aggressive behavior problems. Dodge, K.A, Laird, R., Lochman, J.E., and Zelli, A. and Conduct Problems Prevention Research Group. Multidimensional Latent-Construct Analysis of Children's Social Information Processing Patterns: Correlations with Aggressive Behavior Problems. Psychological Assessment, 14(1), pp. 60-73, 2002.

Peer Rejection and Early Conduct Problems

Peer rejection and aggression in the early school years were examined for relevance to early conduct problems. A sample of 657 children from 4 geographical locations was followed from 1st through 4th grades. Peer rejection in 1st grade added incrementally, over and above the effects of aggression, to the prediction of early conduct problems in grades 3 and 4. Peer rejection and aggression in 1st grade were also associated with the impulsive and emotionally reactive behaviors found in older samples. Being rejected by peers after grade 1 marginally added to the prediction of early conduct problems in 3rd and 4th grades, after controlling for 1st-grade attention deficit hyperactivity disorder (ADHD) symptoms and aggression. Peer rejection partially mediated the predictive relation between early ADHD symptoms and subsequent conduct problems. These results support the hypothesis that the experience of peer rejection in the early school years adds to the risk for early conduct problems. Miller-Johnson, S., Coie, J.D., Maumary-Gremaud, A., Bierman, K., and Conduct Problems Prevention Research Group. Peer Rejection and Aggression and Early Starter Models of Conduct Disorder. Journal of Abnormal Child Psychology, 30(3), pp. 217-230, 2002.

The Development of Aggressive-Withdrawn Behavior Profiles

From a sample of 754 first-grade children, those who exhibited 4 behavior problem profiles were identified: aggressive-withdrawn (n = 63, 8%) aggressive only (n = 165, 22%), withdrawn only (n = 94, 12%), and no-problem (n = 432, 57%). Group comparisons revealed that children who became aggressive-withdrawn in first grade exhibited deficits in attention and social skills in kindergarten. Furthermore, these kindergarten deficits contributed to the emergence of aggressive-withdrawn behavior problems in first grade, after accounting for kindergarten levels of aggressive and withdrawn behaviors. In later grades, children who were aggressive-withdrawn in first-grade were more likely than children in any other group to demonstrate poor peer relations and poor academic performance. In addition, kindergarten skill deficits, added to first-grade aggressive and withdrawn behavior problems predicted third-grade social and academic adjustment difficulties. These results document the key role of early inattention and social skill deficits in the prediction of aggressive-withdrawn problem profiles; validate the significance of this problem profile at school entry; and identify potential developmental mechanisms that have implications for preventive interventions. Farmer, A.D., Bierman, K.L., and Conduct Problems Prevention Research Group. Predictors and Consequences of Aggressive-Withdrawn Problem Profiles in Early Grade School. Journal of Clinical Child & Adolescent Psychology, 31(3), pp. 299-311, 2002.

Childcare and School Readiness

The roles of exposure to childcare and quality of parent-child interaction on the development of school readiness and social skills among a low-income, minority sample of kindergarten children (aged 4.8-5.9 yrs) were examined. Findings provide mixed evidence on exposure to childcare, with earlier entry into childcare predicting higher levels of social skills and increased time per week in childcare predicting lower levels of social skills development. Childcare exposure had positive relationships with other readiness-related outcomes after accounting for demographic characteristics of children and their families. Parent-child interactions that were structured and responsive to the child's needs and emotions were positively related to the development of school readiness, social skills, and receptive communication skills development after accounting for demographic characteristics and childcare exposure. Connell, C. M. and Prinz, R. J. The Impact of Childcare and Parent-child Interactions on School Readiness and Social Skills Development for Low-income African American Children, Journal of School Psychology, 40(2), pp. 177-193, 2002.

Elementary School Alcohol, Tobacco and Marijuana Use Increases Middle School Use

Most drug-use data come from cross-sectional surveys that do not allow assessment of the seriousness of early experimentation on later use. This study utilized longitudinal data to assess whether ATOD use in elementary school has serious implications for continued ATOD use in middle school and beyond. Longitudinal analyses were conducted on questionnaire data from 331 middle school students who had previously provided ATOD-use data during elementary school. The sample of students was ethnically and geographically diverse, including students from a range of low socioeconomic status backgrounds living in rural, urban or inner-city environments. Middle school alcohol use was almost three times as likely to occur if alcohol use occurred in elementary school (OR = 2.94, $p < .001$). Elementary school use of tobacco and marijuana also greatly increased the likelihood of middle school use of these substances (OR = 5.35, $p < .001$ and OR = 4.25, $p < .05$, respectively). This study indicates that early use of ATOD is associated with greatly increased odds of later use, pointing to the importance of drug prevention programs; preventive interventions designed for use in pediatric practice settings should commence no later than elementary school. Wilson, N., Battistich,V., Syme, L., and Boyce, W.T. Does Elementary School Alcohol, Tobacco, and Marijuana Use Increase Middle School Risk? Journal of Adolescent Health, 30, pp. 442-447, 2002.

Many U.S. Middle Schools Continue to Implement Untested or Ineffective Prevention Curricula

School-based curricula constitute the nation's primary means of addressing the prevention of youth substance abuse. Despite an abundance of positive evaluative evidence concerning the effectiveness of a number of school-based substance use prevention curricula, many of the nation's middle schools continue to implement curricula that are either untested or ineffective. Respondents comprised the lead staff who implemented substance use prevention in a representative sample of 1,905 of U.S. public and private middle school schools. A self-administered survey indicated that only 26.8% of all schools used at least 1 of 10 effective curricula. However, few

school or respondent characteristics were related to program implementation. Results demonstrate a considerable gap between our understanding of effective curricula and current school practice. Ringwalt, C., Ennett, S, Vincus, A, Thorne, J, Rohrback, L.A., and Simons-Rudolph, A. The Prevalence of Effective Substance Use Prevention Curricula in U.S. Middle Schools. Prevention Science, 3(4), pp. 257-265, 2002.

Effects of Active Parental Consent on Sample Bias

This article reports the effect of active parental consent on sample bias among rural 7th graders participating in a drug abuse prevention trial. Students obtaining active consent from their parents to complete the survey were of higher academic standing, missed fewer days of school, and were less likely to participate in the special education school programs compared to students that did not return a parental consent form. However, students with consent were not significantly different from students whose parents actively declined. The sample obtained under active parental consent represents students less at-risk for problem behaviors than would be obtained under passive consent procedures. Henry, K.L., Smith, E., and Hopkins, A. The Effects of Active Parental Consent on the Ability to Generalize the Results of an ATOD Prevention Trial to Rural Adolescents. Evaluation Review, 26(6), pp. 425-435, 2002.

Optimal Dynamic Treatment Regimes

A dynamic treatment regime is a list of decision rules, one per time interval, for how the level of treatment will be tailored through time to an individual's changing status. That is, dynamic treatment regimes are individually tailored treatments that are designed to provide treatment to individuals only when and if they need the treatment, explicitly incorporating the heterogeneity in need for treatment across individuals and the heterogeneity in need for treatment across time within an individual. In a dynamic treatment regime, decision rules for how the dosage level and type would vary with time are specified before the beginning of treatment; these rules are based on time-varying measurements of subject-specific need. Dynamic treatment regimes are attractive to public policy makers because they treat only subjects who show a need for treatment, freeing funds for more intensive treatment of the needy, and promise lower non-compliance by subjects due to over treatment. This mathematical paper provides a method for estimating optimal decision rules; rules that when implemented over a time period will produce the highest mean response at the end of the time period. The methodology uses experimental or observational longitudinal data to construct estimators of the optimal decision rules. Murphy, S.A. Optimal Dynamic Treatment Regimes. Journal of the Royal Statistical Society, 65(2), pp. 1-25, 2003.

Early Elementary School Intervention to Reduce Conduct Problems

Children's aggressive behavior and reading difficulties during the early elementary school years are risk factors for adolescent problem behaviors such as delinquency, academic failure, and substance use. This study determined if a comprehensive intervention that was designed to address these risk factors could affect teacher, parent, and observer measures of internalizing and externalizing problems. Drawing from 3 communities, 116 European American and 168 Hispanic kindergarten through 3rd grade children who were identified for aggressiveness or reading difficulties were randomly assigned to a multicomponent intervention or no-intervention control condition. Intervention families received parent training, and children received social behavior interventions and supplementary reading instruction over a 2-year period. Post-intervention playground observations showed that the intervention children displayed less negative social behavior than controls. At 1-year follow-up, treated children showed less teacher-rated internalizing and less parent-rated coercive and antisocial behavior than controls. Barrera, M.J.R., Biglan, A., Taylor, T.K., Gunn, B. K., Smolkowski, K., Black, C., Ary, D.V., and Fowler, R.C. Early Elementary School Intervention to Reduce Conduct Problems: A Randomized Trial with Hispanic and Non-Hispanic Children. Prevention Science, 3(2), pp. 83-94, 2002.

Will the 'Principles of Effectiveness' Improve Prevention Practice? Early Findings From a Diffusion Study

This study examines adoption and implementation of the U.S. Department of Education's new policy, the "Principles of Effectiveness," from a diffusion of innovations theoretical framework focusing on the requirement to select research-based programs. Results from a sample of 104 school districts in 12 states indicate that many districts appear to be selecting research-based curricula, but that the quality of implementation was low. Only 19% of the responding district coordinators

indicated that schools were implementing a research-based curriculum with fidelity. Common problems included lack of teacher training, lack of requisite materials, use of some but not all of the required lessons or teaching strategies, and failure to deliver lessons to age-appropriate student groups. This study represents the first attempt to assess the quality of implementation of research-based programs as required by the SDFS Principles of Effectiveness. The authors conclude that low levels of funding, inadequate infrastructure, decentralized decision making and lack of program guidance contribute to slow progress in improving school-based prevention. Hallfors, D. and Godette, D. Health Education Research, 17(4), pp. 461-470, 2002.

The Quality and Inaccessibility of Local and State School-Based Substance Use Surveys Limits their Usefulness

School-based substance use surveys are an important data source for prevention and evaluation researchers, but access to students has become progressively restricted by schools. Because almost all states and many districts conduct their own regular surveys, archival data are a potential resource for informed policy and practice decisions. This study successfully collected substance use survey data from 69 of 105 targeted school districts located in 12 states. Results indicate that the availability, and quality of extant data currently limit their usefulness. Hallfors, D. and Iritani, B. Local and State School-Based Substance Use Surveys - Availability, Content, and Quality. Evaluation Review, 26(4), pp. 418-437, 2002.

How are Community Coalitions 'Fighting Back' against Substance Abuse, and are they Winning?

This paper examines the strategies that coalitions in a large national demonstration program (Fighting Back) chose to develop, the degree to which they implemented these strategies, and evidence regarding their effectiveness. Coalition strategy implementation was coded and ranked for 12 Fighting Back sites. Effect sizes (intervention over time) for outcomes related to substance use, alcohol and other drug treatment, and community/prevention indicators were ranked by site. Based on rank order correlations to test three directional hypotheses, the article compares strategy dose to outcomes. None of the hypotheses was supported. Strategies aimed at youth or community/prevention outcomes showed no effects; while strategies to improve adult-focused outcomes showed significant negative effects over time, compared to matched controls. Coalitions with a more comprehensive array of strategies did not show superior benefits, and increasing the number of high-dose strategies showed a significant negative effect on overall outcomes. The authors conclude that comprehensive community coalitions are intuitively attractive and politically popular, but the potential for adverse effects must be considered, and that efforts to evaluate implementation processes and strategies with theoretically corresponding outcomes are a critical but neglected aspect of prevention research. Hallfors, D., Hyunsan, C., Livert, D., and Kadushin, C. American Journal of Preventive Medicine, 23(4), pp. 237-245, 2002.

An Early Community-Based Intervention for the Prevention of Substance Abuse and Other Delinquent Behavior

The results of a risk-reduction intervention strategy versus a standard intervention approach in the treatment of inner-city youth at high risk of adopting a deviant lifestyle were examined at baseline and 1-year follow-up using information provided by 408 youth (males and females, aged 9-17 years at interview) admitted to 2 community-based Baltimore City "Youth Bureaus." Bureaus offered counseling services for neighborhood youth referred for delinquent and other problematic behavior. One bureau served as the experimental intervention clinic and another as the control, or standard intervention clinic. Outcome measures involved substance abuse, sexual activity, contact with juvenile authorities, and delinquent activity, including violence-related activity. Regression analyses of outcome measures revealed significant differential results for delinquent activity, favoring the intervention condition. Hanlon, T.E., Bateman, R.W., Simon, B.D., O'Grady, K.E., and Carswell, S.B. Journal of Youth & Adolescence, 31(6), pp. 458-471, 2002.

A Self-Instructed Curriculum for Indicated Adolescent Drug Abuse

Self-instruction programming often is used to help youth that are at high risk for dropout and drug abuse in completing their high school education, and is a method of choice among educators at alternative high schools. The justification, development and impact of one self-instruction program, Project Towards No Drug Abuse (TND) is described. Keys to effective programmed self-learning are examined. Health-educator led, self-instruction, and standard care control conditions were compared on

knowledge change, and the 2 program conditions were compared on process ratings; 572 students completed surveys. A sample of high-school students attended an average of 66% of the sessions in the health educator-led condition, whereas students completed an average of 83% of the self-instruction sessions. The self-instruction condition was easy to implement, provided better implementation, and resulted in learning as great as the health educator condition. However, students rated the health educator condition more positively. Sussman, S., Dent, C.W., Craig, S., Ritt-Olsen, A., and McCuller, W.J. Development and Immediate Impact of a Self-instructed Curriculum for an Adolescent Indicated Drug Abuse Prevention Trial. Journal of Drug Education, 32(2), pp. 121-137, 2002.

Project Towards No Drug Abuse: A Review of the Findings and Future Directions

This paper provides a review of the evidence from 3 experimental trials of Project Towards No Drug Abuse (TND), a senior-high-school-based drug abuse prevention program. Theoretical concepts, subjects, designs, hypotheses, findings, and conclusions of these trials are presented. A total of 2,468 male and female high school youth from 42 schools in southern California were surveyed. The Project TND curriculum shows reductions in the use of cigarettes, alcohol, marijuana, hard drugs, weapon carrying, and victimization compared to controls. Most of these results were replicated across the 3 trials examined. Project TND is an effective drug and violence prevention program for older teens, at least for one-year follow-up. Sussman, S., Dent, C.W., and Stacy, A.W. American Journal of Health Behavior, 26(5), pp. 354-364, 2002.

Influence of a Substance-Abuse-Prevention Curriculum on Violence-Related Behavior

This study tested the impact of a school-based substance-abuse prevention program, Project Towards No Drug Abuse (TND), on risk for violence. Logistic regression analyses tested whether victimization, perpetration, or weapon carrying differed for intervention students relative to control students in a sample of 850 continuation (high-risk) high school students (aged 14-19 years) who were followed over 12 months. Results showed a higher risk for victimization among male control students. No intervention effect was observed for female students or for perpetration among males. The findings provide limited support for a generalization of TND's preventive effect. Simon, T.R., Sussman, S., Dahlberg, L.L., and Dent, C.W. American Journal of Health Behavior, 26(2), pp. 103-110, 2002.

Modeling Behavior Problems in Elementary-Grade Children

Youth problem behaviors such as drug use, delinquency, poor academic achievement and truancy are related, and often co-occur. Problem behavior theory (Jessor & Jessor, 1977) suggests that these disparate norm-violating behaviors reflect an underlying problem behavior syndrome. This study uses data from an ongoing longitudinal study to explore the application of a general theory of problem behavior among adolescents in fifth and sixth grades (N=1040). Confirmatory factor analysis including hierarchical latent factor models was used to examine the structure of problem behaviors that include school problems, aggression, delinquency, and substance use. Five measurement models of problem behaviors were tested, ranging from a single-factor model to a four-factor model and a second-order model. Results support the model that includes specific factors related to school problems, aggression, delinquency and substance use, and a higher order problem behavior factor. These results have implications for how predictors of problem behaviors are modeled at this age. The unique aspects of the higher order model suggest that there may be slightly different pathways to specific problems. It would therefore be useful to include both specific and general paths when examining predictors of problem behaviors at this age. For example, school bonding may have a general effect on deviance, as well as a specific effect on school problems. Modeling both general and specific effects is possible given the good fit of a second-order model as a measure of problem behaviors. Kim, S., Harachi, T.W., and Catalano, R.F., The Structure of Aggression, Delinquent Behaviors, Substance Use and School Problems in Elemenatry-grade Children. Korean Journal of Social Welfare Studies, 19, pp. 51-70, 2002.

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

Research Findings - Services Research

Differences Between Ecstasy-Using and Non-using Methamphetamine Users

The researchers considered ecstasy use within its common poly-drug context (specifically with methamphetamine [MA]), examining differences between Ecstasy-using and non-using subgroups of clients treated for MA use, and exploring the relationship of Ecstasy use to selected treatment outcomes. Ecstasy+MA users differed from those using MA alone, in that those who have not used Ecstasy primarily in terms of socio-demographics (higher income, fewer children), substance abuse behaviors and motivators (lifetime history of more types of drugs, more likely to report use of Ecstasy to enhance sex, more drug-related problems), lifestyle (more likely to have had same-sex sex partners), and treatment characteristics (younger at admission, less likely to complete treatment). Subjects using ecstasy had significantly lower rates of treatment completion, but the actual time to relapse did not differ from the MA using population. These results suggest that using ecstasy compounds the deleterious effects of methamphetamine and compromises access to and adherence to treatment. Brecht, M.L., and von Mayrhauser, C. Journal of Psychoactive Drugs, 34(2), pp. 215-223, April-June 2002.

Mental Health Problems and Sexual Abuse among Adolescents in Foster Care: Relationship to IV Risk Behaviors and Intentions

Although adolescents in foster care present with multiple psychosocial and mental health problems that individually are associated with increased risk for HIV, few studies have examined the interrelationships among these factors. These authors examined sexual abuse histories and mental health problems among 343 youths in foster care to determine associations with HIV-risk behaviors and behavioral intentions. Of the sample, 25% reported internalizing behaviors (withdrawal, somatic complaints, depression), 28% reported externalizing behaviors (delinquency, aggression), and 37% reported prior sexual abuse. Multivariate analyses using simultaneous entry of variables, and controlling for demographic variables and behavioral intentions, showed externalizing behaviors as having the strongest relationship with both HIV risk behaviors and behavioral intentions. Moreover, there was a significant race by gender interaction, with Caucasian females engaging in more risky behaviors than their male counterparts and youths of color. This study begins to address the comparatively understudied issue of the empirical interrelationships among psychosocial problems and HIV risk behaviors in foster care children. Auslander, W.F., McMillen, J.C., Elze, D., Thompson, R., Jonson-Reid, M., and Stiffman, A. AIDS & Behavior, 6(4), pp. 351-359, December 2002.

Factors Associated with Completion of a Drug Treatment Court Diversion Program

Drug Treatment Courts are a relatively new effort to provide treatment instead of punitive incarceration for certain drug offenders. The researchers analyzed initial data from a longitudinal study of drug court outcomes in Delaware to identify factors associated with successful completion of a drug treatment program for first-time offenders. The strongest predictors of success were factors associated with social stakeholder values, especially those involving employment. Factors associated with program completion included race, education, and frequency of drug use. While the overall success of drug courts continues to be documented, these data suggest that success varies with individual characteristics. This study is an initial step toward understanding the influence of individual offender characteristics on the outcomes of Delaware's drug court system. This knowledge is essential for determining

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appropriate candidacy for drug court substance abuse treatment and developing effective treatment interventions and resources for offenders. Butzin, C.A., Saum, C.A., and Scarpitti, F.R., Substance Use and Misuse, Fall 2002.

Pathways to Long-term Recovery: A Preliminary Investigation

Recovery from addiction is a lifelong process. A large body of empirical data exists on the short-term effectiveness (one to two years) of various treatment modalities, yet little is known about recovery processes over time. This is unfortunate because treatment gains are often short-lived and even multiple treatment episodes do not always succeed in breaking the addiction cycle. Further, treatment represents only one path to recovery. This article reports on a study of individuals in long-term recovery from substance abuse (median = 12 years) and examines the factors they cite as important in establishing and maintaining their recovery status. Key factors reported were social and community support, affiliation with 12-Step organizations and negative consequences of substance use. This study points to the importance of prosocial networks in supporting continued abstinence in the community. Laudet, A.B., Savage, R., and Mahmood, D. J Psychoactive Drugs, 34(3), pp. 305-311, July-September 2002.

Case Management as a Therapeutic Enhancement: Impact on Post-treatment Criminality

The researchers examined proximal (aftercare participation) and distal (severity of legal problems) measures of treatment outcomes among 453 veterans who received substance abuse treatment and were randomly assigned to case management and non-case management. The results of multivariate analyses showed that case-managed subjects stayed longer in aftercare services than non-case managed clients, and the longer these clients stayed in post-treatment aftercare, the less they participated in criminal activity. The length of aftercare participation was also positively associated with employment and initial readiness for treatment. This study adds to the evidence that motivation for treatment and case management services are essential components to standards of care leading to positive client outcomes. Siegal, H.A., Li, L., and Rapp, R.C. J Addictive Disorders, 21(4), pp. 37-46, 2002.

UpDate: State Report-Integration and Its Discontents: Substance Abuse Treatment in the Oregon Health Plan

With the creation of the Oregon Health Plan (OHP) in 1994, Oregon placed its Medicaid program under a managed care system. This paper examines the managed care practices of seven health plans serving OHP enrollees between 1996 and 1998. Results indicated that the original plan to integrate substance abuse treatment services with physical care for OHP 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 incentives for physicians to refer clients to substance abuse treatment. This research provides important information related to the impact of managed care practices on substance abuse treatment services for Medicaid recipients. Laws, K.E., Gabriel, R.M., and McFarland, B., Health Affairs, 21(4), pp. 284-289, Jul-Aug, 2002.

Coping Among Individuals Seeking Private Chemical Dependence Treatment: Gender Differences and Impact on Length of Stay in Treatment

Length of stay in treatment and coping skills predict chemical dependence and abuse treatment outcomes. The researchers explored the interaction of coping strategies and length-of-stay in treatment, while paying particular attention to the effect of gender among 747 (433 men, 314 women) individuals who entered chemical dependence and abuse treatment in a private, managed care facility. Women reported using more emotional discharge (behavioral attempts to reduce tension by expressing negative feelings), cognitive avoidance (cognitive attempts to avoid thinking realistically about problems), resigned acceptance (cognitive attempts to react to problems by accepting them), and seeking support/guidance (behavioral attempts to seek information, guidance, or support) than men. The gender differences for emotional discharge disappeared after the variables of depressive symptom and drug problem severities were controlled. Greater use of seeking alternative rewards (behavioral attempts to participate in substitute activities and create new sources of satisfaction), less use of emotional discharge, and older age were significant predictors of longer length of stay, with no gender differences found. This study provides evidence for identifying and decreasing the use of emotional discharge early in treatment, possibly through the use of intervention strategies such as anger

management, cognitive restructuring, or motivational interviewing, as well as encouraging participation in alternative activities. Kohn, C.S., Mertens, J.R., and Weisner, C.M. Alcoholism-Clinical and Experimental Research, 26(8), pp. 1228-1233, 2002.

Selecting Data Sources for Substance Abuse Services Research

In this article, researchers discuss the strengths and weaknesses of using different sources of data in the conduct of alcohol and drug abuse services research. Four different data sources commonly used in substance abuse services research are described: surveys of organizations, medical records, claim and encounter data, and program-level administrative data. For each, information is provided on where to obtain data, how each type has been used, and the advantages and challenges of each. This overview can help investigators to think more critically about the datasets they now use; providers to understand the types of data sources most appropriate for specific research questions so as to participate more fully in research; and policy makers to interpret correctly the study results based on different types of data. Moreover, it should foster better communication among these stakeholders in collaborative projects to improve the effectiveness of services for people with addictions. Garnick, D.W., Hodgkin, D., and Horgan, C.M. J Subst Abuse Treat, 22(1), pp. 11-22, 2002.

Managed Care Plans' Requirements for Screening for Alcohol, Drug, and Mental Health Problems in Primary Care

Researchers sought to determine managed care organizations' (MCOs) requirements for screening for alcohol, drug, or mental health problems in primary care settings. A telephone survey was used to gather information on the three largest commercial products offered by MCOs. Products included health maintenance organizations, preferred provider organizations, and point-of-service plans. Managed care organizations were asked whether their products required screening for alcohol, drug, or mental health problems in primary care settings. Chi-square tests were performed to ascertain whether screening requirements, the distribution of practice guidelines, and the topics addressed in those guidelines varied by product type and contracting with specialty behavioral health vendors. The data were weighted to produce national estimates. Only about 15% of the products surveyed required any alcohol, drug, or mental health screening by primary care practitioners. Slightly more than half of all the products surveyed distributed practice guidelines that addressed mental illness, and about one third distributed substance abuse practice guidelines. Although the feasibility, utility, and effectiveness of screening are increasingly recognized, few MCOs currently require alcohol, drug, or mental health screening by primary care physicians in any of their product types. Garnick, D.W., Horgan, C.M., Merrick, E.L., Hodgkin, D., Faulkner, D., and Bryson, S. Am J Manage Care, 8(10), pp. 879-88, August 2002.

Program Retention and Perceived Coercion in Three Models of Mandatory Drug Treatment

Despite the proliferation of drug courts and other mandatory treatment models, few studies have compared the impact of different program features. This study compared three groups of clients (N = 330) mandated to the same long-term residential treatment facilities. Study participants were referred from two highly structured programs or from more conventional legal sources, such as probation or parole agents. Analyses showed that these clients varied substantially in their perceptions of legal pressure, and these perceptions generally corresponded to the programs' different coercive policies and practices. Retention analyses confirmed that the odds of staying in treatment for six months or more were nearly three times greater for clients in the most coercive program compared to clients in the third group. Results support the use of structured protocols for informing clients about legal contingencies of participation and how participation will be monitored, and developing the capacity to enforce threatened consequences for failure. Young, D., and Belenko, S. Journal of Drug Issues, 32(1), pp. 297-328, Winter 2002.

Improving Service Delivery to the Dually Diagnosed in Los Angeles County

Service delivery to dually diagnosed individuals remains problematic in many communities because of entrenched administrative structures that maintain the separation of mental health and substance abuse treatment systems. This article describes efforts to improve service delivery to dually diagnosed individuals in Los Angeles County by increasing communication, coordination, and collaboration across the two treatment systems. Findings are presented on the relationships among

program models of service delivery, treatment orientations of programs, and interactions with other service providers to the dually diagnosed. Results showed that drug treatment programs that adhered more closely to an integrated model of service delivery received more patient referrals from case management outreach teams and that programs with a stronger counseling approach to treatment had more linkages with other service providers. Knowledge gained from research on these differing models of service delivery can be combined with new clinical advances to improve service delivery to the dually diagnosed. Grella, C.E., and Gilmore, J. Journal of Substance Abuse Treatment, 23(2), pp. 115-122, 2002.

Predictors of Drug Abuse Treatment Entry Among Crack-cocaine Smokers

The goal of this study was to identify factors that predict drug abuse treatment program entry among a community sample of 430 crack-cocaine users. Subjects were recruited using a targeted sampling method, and they responded to interviewer-administered questionnaires at 6 month intervals over a 3-year period. At baseline, 41% (n = 174) reported they had never been in a drug abuse treatment program. During the observation period, 38% (n = 162) reported they had entered a program. Of these, 44% (n = 71) reported that their treatment was court-ordered. Slightly more than 25% (n = 44) entered treatment for the first time. A host of variables, including individual characteristics, frequency and duration of crack use, frequency of drunkenness, Addiction Severity Index (ASI) family/social, medical, and psychiatric status composite scores, perceived need for treatment, history of treatment, and medical insurance coverage, were explored. The results of Cox proportional hazards model suggested that younger people, users with more severe legal problems, people who perceived a need for treatment, and individuals with prior treatment experience had a greater likelihood of entering treatment. Developing a strategy to practically apply these findings may facilitate treatment entry for a population involved with a dangerous and debilitating drug. Siegal, H.A., Falck, R.S., Wang, J.C., and Carlson, R.G. Drug and Alcohol Dependence, 68(2), pp. 159-166, 2002.

Transporting a Research-based Adolescent Drug Treatment into Practice

This article describes the key ingredients and processes of transporting an empirically supported, research-developed family therapy for adolescent drug abusers, Multidimensional Family Therapy (MDFT), into an intensive day treatment program. Using the same systems change principles that guide this treatment approach, the technology transfer process is a collaborative, multidimensional, systemic intervention aimed at changing organizational structures, and attitudinal and behavioral patterns with multiple staff members at several program levels. This article describes: (1) the conceptual and empirical basis for these technology transfer efforts; (2) the technology being adapted and transferred; and (3) the critical events and processes that have shaped the transfer of MDFT into this program. The authors discuss the process and outcomes using Simpson's model of organizational change and specify the implications of this experience for the expansion of current conceptualization of technology transfer. Liddle, H.A., Rowe, C.L., Quille, T.J., Dakof, G.A., Mills, D.S., Sakran, E., and Biaggi, H. J Subst Abuse Treat, 22(4), pp. 231-243, June 2002.

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

This study addresses a gap in the adolescent substance abuse treatment literature by examining the long-term outcomes of a family-based treatment model. Eighty of 118 substance-abusing juvenile offenders provided follow-up data 4 years after participating in a randomized clinical trial comparing Multisystemic Therapy (MST) 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 evidence that MST can produce favorable long-term reductions in antisocial and drug using behavior of substance-abusing juvenile offenders. This information adds to the body of knowledge regarding appropriate treatment modalities for adolescent 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.

The Relationship Between Sexual and Physical Abuse and Substance Abuse

Consequences

The authors examined the relation between a history of physical and sexual abuse and drug and alcohol related consequences. Cross-sectional data came from 359 male and 111 female patients recruited from an inpatient detoxification unit. The Inventory of Drug Use Consequences was used to measure 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. The results of bivariate and multivariate analyses indicated that physical and sexual abuse was associated with more substance abuse consequences. For men, age 17 years or younger 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.

Injury Among Detoxification Patients: Alcohol Users' Greater Risk

The authors examined injury prevalence, and the impact of alcohol use on injury, among alcohol- and drug-dependent persons. Four hundred seventy (470) patients at a detoxification unit enrolled in a prospective cohort study. They were interviewed at baseline and follow-up (6, 12, 28, 24 months) to determine prevalence of injury. Overall, 24% reported at least one serious injury during the six-month period before detoxification. Similarly, about 20% had serious injury during each of the 6-month follow-up periods. Injury in the past six months was highest among the 63% of subjects who reported alcohol as a drug of choice, even after controlling for potential confounds. Analysis of 2-year follow-up data revealed a similar association, after controlling for baseline injury and alcohol consumption. The authors conclude that injury is a serious problem for a substantial proportion of patients who undergo detoxification, particularly those with alcohol dependence. This marked risk for injury persisted for 24 months after detoxification. This study suggests that patients at detoxification, particularly those with alcohol problems, represent a high-risk population for injury that may benefit from interventions to reduce these preventable complications. Rees, V.W., Horton, N.J., Hingson, R.W., Saitz, R., and Samet, J.H. Alcoholism: Clinical and Experimental Research, 26(2), pp. 212-217, February 2002.

Professional Satisfaction Experienced When Caring for Substance-abusing Patients

This survey aimed to describe and compare the satisfaction, attitudes, and practices regarding patients with addictions among 144 resident and faculty primary care physicians. Of the sample, 40% of physicians used formal screening tools to assess substance abuse, and 24% asked patients' family history. Physicians were less likely ($P<.05$) to experience at least a moderate amount of professional satisfaction caring for patients with alcohol (32% of residents, 49% of faculty) or drug (residents 30%, faculty 31%) problems than when caring for patients with hypertension (residents 76%, faculty 79%). Interpersonal experience with addictions was common (85% of faculty, 72% of residents) but not associated with attitudes, practices, or satisfaction. Positive attitudes toward addiction treatment (adjusted odds ratio [AOR], 4.60; 95% confidence interval [95% CI], 1.59 to 13.29), confidence in assessment and intervention (AOR, 2.49; 95% CI, 1.09 to 5.69), and perceived responsibility for addressing substance problems (AOR, 5.59; 95% CI, 2.07 to 15.12) were associated with greater satisfaction. These results show that professional satisfaction caring for patients with substance problems is lower than that for other illnesses and suggest that addressing physician satisfaction may improve care for patients with addictions. Saitz, R., Friedmann, P.D., Sullivan, L.M., Winter, M.R., Lloyd-Travaglini, C., Moskowitz, M., and Samet, J.H. Journal of General Internal Medicine, 17, pp. 373-376, 2002.

Relationship Between Tobacco Smoking and Medical Symptoms Among Cocaine-, Alcohol- and Opiate-Dependent Patients

This study examined the relation between tobacco smoking and medical symptoms among 87 cocaine-, 98 opiate-, and 81 alcohol-dependent individuals receiving outpatient treatment. Smoking status was assessed and medical symptoms were recorded using a standardized 134-item self-report instrument (MILCOM). Almost 79% of patients were tobacco smokers. Analysis of variance revealed a main effect of tobacco smoking on medical symptoms. Smokers reported significantly more symptoms compared to non-smokers on the total scale and on the respiratory, cardiovascular, gastrointestinal, and nose/throat subscales. There was a significant interaction between tobacco smoking and substance abuse with respect to medical

symptoms, such that opiate- and alcohol-dependent patients who smoked reported more medical symptoms than those who did not, but cocaine users who smoked reported fewer symptoms than those who did not smoke. The findings support the link between smoking and medical problems among substance abusers, but suggest that the effects are not uniform across substances of abuse. Patkar, A.A., Sterling, R.C., Leone, F.T., Lundy, A., and Weinstein, S.P. The American Journal on Addictions, 11, pp. 209-218, 2002.

Tobacco and Alcohol Use and Medical Symptoms Among Cocaine Dependent Patients

The authors investigated the relations between smoking and alcohol use, and medical symptoms in 125 cocaine-dependent patients. Study participants were assessed for smoking, alcohol use, and medical problems using the MILCOM, a standardized self-report instrument. Medical symptoms were compared among non-smokers, moderate smokers (<10 cigarettes/day), and heavy smokers (>10 cigarettes/day) using partial chi-square statistics. Similar comparisons of medical symptoms were made between alcohol users (>2 drinks/day) and nonusers. Contrary to expectation, there were no significant differences between non-smokers, moderate smokers, and heavy smokers across most of the 14 major medical systems assessed. However, regardless of level of cocaine use, non-smokers reported the fewest symptoms on the general subscale, while moderate smokers reported the most nose/throat and respiratory symptoms among the three groups. As expected, significant relations were observed between medical symptoms and alcohol use. Alcohol users reported more respiratory, cardiovascular, digestive, head/neck, eye, and general medical symptoms than non-users. Although the findings generally support the link between alcohol use and medical problems, the relation between medical symptoms and smoking among cocaine patients may be more complex than that observed in the general population. Patkar, A.A., Lundy, A., Leone, F.T., Weinstein, S.P., Gottheil, E, and Steinberg, M. Substance Abuse, 23, pp. 105-114, 2002.

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Research Findings - Intramural Research

Development and Plasticity Section, Cellular Neurobiology Research Branch

Reduction of Synapsin in the Hippocampus of Patients with Bipolar Disorder and Schizophrenia Several studies suggest that decreased expression of presynaptic proteins may be characteristic of schizophrenia. We examined one such protein, synapsin, in schizophrenia and bipolar disorder. Samples of hippocampal tissue from controls (n = 13), patients with schizophrenia (n = 16), or bipolar disorder (n = 6), and suicide victims (n = 7) were used. The membrane and cytosolic fractions were analyzed by Western immunoblotting for synapsin using an antibody that detects synapsin Ia, IIa, and IIIa proteins. Synaptophysin was also measured for comparison. Total synapsin was decreased significantly in patients with schizophrenia (P = 0.034) and in bipolar disorder (P = 0.00008) as compared to controls. The synapsin/ synaptophysin ratios were decreased in schizophrenia and bipolar disorder, and additionally in suicide victims (P = 0.014). Age, postmortem interval, percentage of protein extracted, and pH of brain were not different between groups. No changes in total synapsin or synaptophysin in the hippocampus were produced by injecting rats with either lithium or haloperidol for 30 days. Reductions in synapsin in both patients with schizophrenia (synapsin IIa and IIIa) and bipolar disorder (synapsin Ia, IIa and IIIa) imply that altered or reduced synaptic function in the hippocampus may be involved in these disorders. Vawter, M.P., Thatcher, L., Usen, N., Hyde, T.M., Kleinman, J.E., and Freed, W.J. Molecular Psychiatry, 7, pp. 571-578, 2002.

Transplantation of M213-2O Cells with Enhanced GAD(67) Expression into the Inferior Colliculus Alters Audiogenic Seizures The purpose of the present study was to examine the effects of GABA-producing cell transplants on audiogenic seizures (AGS). The M213-2O cell line was derived from fetal rat striatum and has GABAergic properties. This cell line was further modified to express human GAD(67) and produce elevated levels of GABA. The present study compares the effects of parent M213-2O cell transplants with those of GAD(67)-modified M213-2O cells in AGS-prone Long-Evans rats. Two weeks following implantation of engineered cells, latency to AGS-typical wild running was increased compared to nonimplanted subjects. Survival of the transplanted cells was confirmed by immunochemical labeling of GAD(67) and Epstein-Barr virus nuclear antigen. These findings support the use of GABA-producing cell lines to modify seizure activity. Ross, K.C., Waldman, B.C., Conejero-Goldberg, C., Freed, W., and Coleman, J.R. Experimental Neurology, 177, pp. 338-340, 2002.

Microarray Analysis of Gene Expression in the Prefrontal Cortex in Schizophrenia: A Preliminary Study Microarray studies can be used to examine expression levels for large numbers of genes simultaneously and may be applied to identify genes involved in schizophrenia. A microarray with 1127 brain-relevant genes was used to screen relative gene expression in the dorsolateral prefrontal cortex (DLPFC) from three pools of patients with schizophrenia (n=15) and three matched control pools (n=15). Pooling of tissue samples was employed as a strategy to detect changes in gene expression that are consistently found across individual cases of schizophrenia. Differences in gene expression were examined by z-ratios in addition to traditional normalized ratios. Three genes that showed consistently decreased expression in schizophrenia by both z-ratio differences and decreased normalized numerical ratios were identified. These were histidine triad nucleotide-binding protein (HINT), ubiquitin conjugating enzyme E2N (UBE2N) and glutamate receptor, ionotropic, AMPA 2 (GRIA2). Moreover, HINT gene expression was decreased to a similar degree in a prior study. In addition, a decrease in AMPA receptor expression is consistent with a decrease in glutamate synaptic function. These results are subject to

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limitations based on variations inherent to human subjects and tissue samples, possible effects of neuroleptic treatment, and the requirement for verification using independent techniques. Vawter, M., Crook, J., Hyde, T., Kleinman, J., Weinberger, D., Becker, K., and Freed, W. Schizophrenia Research, 58, pp. 11-20, 2002.

Molecular Neuropsychiatry Section, Cellular Neurobiology Research Branch

Analysis of Ecstasy (MDMA)-induced Transcriptional Responses in the Rat Cortex 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) is a popular drug of abuse. MDMA is pharmacologically classified as an entactogen because of its affinities to classical hallucinogens and stimulants. Oral ingestion of a single dose of the drug is associated with euphoria, elevated self-confidence, and heightened sensory awareness in humans. Evidence for neurotoxicity in the human serotonin (5-HT) system has been provided. In rats, a single injection of MDMA induces hyperthermia and formation of reactive oxygen species. These effects may cause MDMA-associated, long-term 5-HT depletion, with the cortex being quite sensitive to the biochemical effects of MDMA. It has been suggested that these MDMA effects may be associated with molecular changes in this brain region. To test these ideas, IRP researchers have made use of the cDNA array analysis, which can provide a more global view of the molecular changes secondary to MDMA injections. Results show that the genes regulated by MDMA encode proteins that belong to signaling pathways, transcription regulators, or xenobiotic metabolism. Observations indicate that cortical cells respond to the acute administration of MDMA by modulating transcription of several genes that might lead to long-term changes in the brain. Thiriet, N., Ladenheim, B., McCoy, M.T., and Cadet, J.L. FASEB Journal, 16, pp. 1887-1894, 2002.

Dose-related Neurocognitive Effects of Marijuana Use Although about 7 million people in the U.S. population use marijuana at least weekly, there is a paucity of scientific data on persistent neurocognitive effects of marijuana use. In order to determine if neurocognitive deficits persist in 28-day abstinent heavy marijuana users and if these deficits are dose-related to the number of marijuana joints smoked per week IRP iunvestigators administered a battery of neurocognitive tests to 28-day abstinent heavy marijuana abusers. Results showed that as joints smoked per week increased, performance decreased on tests measuring memory, executive functioning, psychomotor speed, and manual dexterity. When dividing the group into light, middle, and heavy user groups, the heavy group performed significantly below the light group on 5 of 35 measures and the size of the effect ranged from 3.00 to 4.20 SD units. Duration of use had little effect on neurocognitive performance. The authors conclude that very heavy use of marijuana is associated with persistent decrements in neurocognitive performance even after 28 days of abstinence. It is unclear if these decrements will resolve with continued abstinence or become progressively worse with continued heavy marijuana use. Bolla, K.I., Brown, K., Eldreth, D., Tate, K., and Cadet, J.L. Neurology, 59, pp. 1337-1343, 2002.

Mice with Partial Deficiency of c-Jun Show Attenuation of Methamphetamine-induced Neuronal Apoptosis The regional distribution of c-Jun expression and of the number of apoptotic cells was compared in various brain areas after methamphetamine administration to mice. Our results showed that there was methamphetamine-induced overexpression of c-Jun in the cortex and striatum but not in the cerebellar cortex. There was an almost totally similar regional appearance of methamphetamine-induced apoptotic cells in the mouse brain; no apoptosis was present in the cerebellum. Additionally, in the neocortical area, more positive signals for c-Jun immunoreactivity were observed in the piriform cortex, an area that also showed more positive terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) signals than the frontal and parietal cortices. These observations suggested that c-Jun might be involved in methamphetamine-induced apoptosis. This idea was confirmed by using heterozygous c-Jun knockout mice that showed much less apoptosis than wild-type controls. In addition, the authors found that the majority of TUNEL-positive cells were also positive for c-Jun-like immunoreactivity in both genotypes. Moreover, methamphetamine-induced caspase-3 activity and PARP cleavage were also reduced in c-Jun heterozygous knockout mice. In contrast, methamphetamine-induced hyperthermia was essentially identical in the two genotypes. When taken together, these data support the hypothesis that c-Jun is involved in methamphetamine-induced apoptosis. Deng, X., Jayanthi, S., Ladenheim, B., Krasnova, I.N., and Cadet, J.L. Molecular Pharmacology, 62, pp. 993-1000, 2002.

cDNA Array Analysis of Gene Expression Profiles in the Striata of Wild-type and Cu/Zn Superoxide Dismutase Transgenic Mice Treated with Neurotoxic Doses of Amphetamine Amphetamine (AMPH) is a drug of abuse that causes the degeneration of striatal dopamine terminals in mammals. Superoxide radicals seem to

participate in AMPH-induced damage because its toxicity is attenuated in Cu/Zn superoxide dismutase transgenic (SOD-tg) mice. To provide a detailed analysis of molecular changes associated with AMPH toxicity, IRP scientists used cDNA arrays consisting of 1176 genes to detect differential changes in gene expression in the striata of wild-type and SOD-tg mice treated with neurotoxic doses of the drug. The authors found 42 genes that showed >1.8-fold changes in at least two consecutive time points during the course of the study and were differentially affected by AMPH in the two genotypes. Specifically, more transcription factors and genes involved in responses to injury/inflammation were affected in wild-type mice after AMPH administration. Some of these stimulant-induced superoxide-dependent alterations in gene expression might affect neuronal functions and promote neuronal damage. Other changes might help to provide some degree of protection against AMPH toxicity. These results support the view that the use of global array analysis of gene expression will help to identify novel molecular mediators of AMPH-induced neurodegeneration. Krasnova, I.N., McCoy, M.T., Ladenheim, B., and Cadet, J.L. FASEB Journal, 16, pp. 1379-1388, 2002.

Molecular Neurobiology Section, Molecular Neurobiology Branch

Knockout Mice Reveal Mechanisms of Drug Reward Over the past year, IRP scientists have followed up on their seminal obeservations regarding elimination of cocaine reward in double knockout mice with deletions of dopamine and serotonin transporters; they now report that mice with combined knockouts of norepinephrine and serotonin transporters display contrastingly ENHANCED cocaine reward and that drugs that block SERT are highly rewarding in DAT knockout mice. Hall, F.S., Li, X.F., Sora, I., Xu, F., Caron, M., Lesch, K.P., Murphy, D.L., and Uhl, G.R. Neuroscience, 115, pp. 153-158, 2002.

Identifying Human Gene Variants for Substance Abuse Vulnerability Over the past year, IRP scientists have identified 42 regions of human DNA that contain variations linked to drug abuse vulnerability. Variations in sixteen of these regions are "powerful" enough that they have been identified in studies from several different laboratories; in studies of individuals addicted to several different substances; and in individuals of several different ethnic backgrounds. Over the past year, IRP scientists have reported new laboratory and analytic technologies that can identify human DNA variants linked to drug abuse vulnerability while providing the maximal possible conservation of confidentiality for these sensitive subjects. Uhl, G.R., Liu, Q.R., and Naiman, D. Trends in Genetics, 18, pp. 420-425, 2002.

Cognition and Pharmacology Section, Neuroimaging Research Branch

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

Preclinical Pharmacology Section/Behavioral Neuroscience Branch

Synergistic Interaction Between Adenosine A2A and Glutamate mGlu5 Receptors: Implications for Striatal Neuronal Function The physiological

meaning of the coexpression of adenosine A2A receptors and group I metabotropic glutamate receptors in GABAergic striatal neurons is intriguing. Here, IRP scientists provide in vitro and in vivo evidence for a synergism between adenosine and glutamate based on subtype 5 metabotropic glutamate (mGluR5) and adenosine A2A (A2AR) receptor/receptor interactions. Colocalization of A2AR and mGluR5 at the membrane level was demonstrated in non-permeabilized HEK-293 cells transiently co-transfected with both receptors by confocal laser microscopy. Complexes containing A2AR and mGluR5 were demonstrated by Western-blotting of immunoprecipitates of either Flag-A2AR or HA-mGluR5 in membrane preparations from co-transfected HEK-293 cells and of native A2AR and mGluR5 in rat striatal membrane preparations. In co-transfected HEK-293 cells a synergistic effect on ERK1/2 phosphorylation and c-fos expression was demonstrated upon A2AR/mGluR5 co-stimulation. No synergistic effect was observed at the second messenger level (cAMP accumulation and intracellular calcium mobilization). Accordingly, a synergistic effect on c-fos expression in striatal sections and on counteracting phencyclidine-induced motor activation was also demonstrated after the central co-administration of A2AR and mGluR5 agonists to rats with intact dopaminergic innervation. The results suggest that a functional mGluR5/A2AR interaction is required to overcome the well-known strong tonic inhibitory effect of dopamine on striatal adenosine A2AR function. Ferre, S., Karcz-Kubicha, M., Hope, B.T., Popoli, P., Burgueno, J., Casado, V., Fuxe, K., Lluis, C., Goldberg, S.R., Franco, R. and Ciruela, F. Proc. Natl. Acad. Sci. USA, 99, pp. 11940-11945, 2002.

Caffeine Induces Dopamine and Glutamate Release in the Shell of the Nucleus Accumbens An increase in the extracellular concentration of dopamine in the nucleus accumbens is believed to be one of the main mechanisms involved in the rewarding and motor-activating properties of psychostimulants, such as amphetamine and cocaine. Using in vivo microdialysis in freely-moving rats, IRP investigators demonstrated for the first time that systemic administration of behaviorally relevant doses of caffeine can preferentially increase extracellular levels of dopamine and glutamate in the shell of the nucleus accumbens. These effects could be reproduced by administration of a selective adenosine A1 receptor antagonist, but not by a selective adenosine A2A receptor antagonist. This suggests that caffeine, due to its ability to block adenosine A1 receptors, shares neurochemical properties with other psychostimulants, which could contribute to the widespread consumption of caffeine-containing beverages. Solinas, M., Ferre, S., You, Z-B., Karcz-Kubicha, M., Popoli, P. and Goldberg, S.R. Journal of Neuroscience 22, pp. 6321-6324, 2002.

Caffeine Potentiates the Discriminative-stimulus Effects of Nicotine in Rats Caffeine and nicotine are the main psychoactive ingredients of coffee and tobacco, respectively, with a high frequency of concurrent use in humans. The aim of the present study was to examine the interaction of caffeine and nicotine in rats trained to discriminate nicotine from saline. Two groups of male Sprague-Dawley rats (n=8 per group) were trained to discriminate 0.4 mg/kg nicotine, SC, from saline under a fixed ratio schedule of food presentation. One group of rats was chronically exposed to caffeine (1.0 mg/ml) dissolved in their drinking water whereas the other group was exposed to tap water. Effects of IP injections of caffeine on nicotine-lever selection were subsequently examined. In separate groups of rats exposed to the same caffeine-drinking or water-drinking regimen, effects of caffeine pretreatment on nicotine plasma levels were evaluated. Although caffeine (1.0-30.0 mg/kg) did not generalize to nicotine when administered alone, it markedly potentiated discriminative-stimulus effects of the threshold dose of nicotine (0.05 mg/kg) in both water- and caffeine-drinking rats. Nicotine plasma levels were, however, not affected by acute or chronic caffeine exposure. Caffeine appears to enhance the discriminative-stimulus effects of the threshold dose of nicotine by a pharmacodynamic rather than a pharmacokinetic interaction. This suggests that caffeine consumption may be a contributing factor in the onset, maintenance of and relapse to tobacco dependence. Gasior, M., Jaszyna, M., Munzar, P., Witkin, J.M. and Goldberg S.R. Psychopharmacology 162, pp. 385-395, 2002.

Psychobiology Section, Medications Discovery Research Branch

Intravenous Cocaine Induced-activity and Behavioral Sensitization in Norepinephrine-, but not Dopamine-transporter Knockout Mice The present studies were designed to determine the respective roles of the norepinephrine (NET) and dopamine transporters (DAT) in the stimulant effects of acute and repeated cocaine utilizing knockout (KO) mice. Mice were habituated to the test environment for sufficient time to ensure equal baselines at the time of cocaine administration. Mice then received cocaine (3-25 mg/kg) intravenously according to a within-session cumulative dose-response design. Cocaine dosing was repeated at 48-hour intervals

for four sessions to assess behavioral sensitization. NET-KO mice exhibited a reduced response to acute cocaine administration compared to wild-type (WT) controls. However, comparable sensitization developed in NET-KOs and WTs. The DAT-KO and DAT-heterozygote (HT) mice displayed no locomotor activation following either acute or repeated cocaine administration. These data suggest a role for the NET in the acute response to cocaine, but no involvement in sensitization to cocaine. In contrast, the DAT appears to be necessary for both the acute locomotor response to cocaine and the subsequent development of sensitization. In addition to existing data concerning the reinforcing effects of cocaine in DAT-KO mice, these data suggest a dissociation between the reinforcing and locomotor stimulant effects of cocaine. Mead, A.N., Rocha, B.A., Donovan, D.M. and Katz, J.L. European Journal of Neuroscience, 15, pp. 514-520, 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. Some effects of the relatively selective DA D2-like antagonist, raclopride were also studied to further assess the role of D2 receptors. 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. A range of doses of cocaine (1.0 - 17 mg/kg), was administered before 15-min test-sessions. Both DA D2R KO and HET mice showed reduced levels of horizontal 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. All three genotypes acquired the discrimination of 10 mg/kg cocaine; tested doses of 1.0 - 10.0 mg/kg produced dose-related increases in the number of cocaine-appropriate responses. Raclopride, at inactive to fully active doses (0.1 - 1.0 mg/kg), did not fully substitute for 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, 163, pp. 54-61, 2002.

Clinical Psychopharmacology Section, Medications Development Research Branch

Salvinorin A, an Hallucinogenic Plant Extract, is a Potent Naturally Occurring Non-nitrogenous Kappa Opioid Selective Agonist Salvia divinorum, whose main active ingredient is the neoclerodane diterpene Salvinorin A, is a hallucinogenic plant in the mint family that has been used in traditional spiritual practices for its psychoactive properties by the Mazatecs of Oaxaca, Mexico. More recently, S. divinorum extracts and Salvinorin A have become more widely used in the U.S. as legal hallucinogens. IRP scientists discovered that Salvinorin A potently and selectively inhibited (3)H-bremazocine binding to cloned kappa opioid receptors. Salvinorin A had no significant activity against a battery of 50 receptors, transporters, and ion channels and showed a distinctive profile compared with the prototypic hallucinogen lysergic acid diethylamide. Functional studies demonstrated that Salvinorin A is a potent kappa opioid agonist at cloned kappa opioid receptors expressed in human embryonic kidney-293 cells and at native kappa opioid receptors expressed in guinea pig brain. Importantly, Salvinorin A had no actions at the 5-HT2A serotonin receptor, the principal molecular target responsible for the actions of classical hallucinogens. Salvinorin A thus represents, to the authors' knowledge, the first naturally occurring nonnitrogenous opioid-receptor subtype-selective agonist. Because Salvinorin A is a psychotomimetic selective for kappa opioid receptors, kappa opioid-selective antagonists may represent novel psychotherapeutic compounds for diseases manifested by perceptual distortions (e.g., schizophrenia, dementia, and bipolar disorders). Additionally, these results suggest that kappa opioid receptors play a prominent role in the modulation of human perception. Roth, B.L., Baner, K., Westkaemper, R., Siebert, D., Rice, K.C., Steinberg, S., Ernsberger, P. and Rothman, R.B., Proc. Natl. Acad. Sci USA, 99, pp. 11934-11939, 2002.

Identification of a Novel Partial Inhibitor of Dopamine Transporter Among 4-Substituted 2-phenylquinazolines Using [125I]RTI-55 to label the DA transporter (DAT), IRP scientists have consistently detected one binding site as well as one component of [3H]DA uptake. Authors report here the identification of a novel partial inhibitor of [3H]DA uptake and DAT binding (SoRI-9804). [125I]RTI-55 binding to the DAT (mouse caudate, rat caudate, HEK cells expressing the cloned DAT), the 5-HT transporter (rat brain) and [3H]DA uptake (rat caudate synaptosomes) were conducted using published procedures. 4-[(Diphenylmethyl)amino]-2-phenylquinazoline (SoRI-9804) was essentially inactive at SERT binding and resolved two DAT binding components in all 3 tissues, having high affinity (mean Ki of 465 nM) for about 40% of the binding sites and an essentially immeasurable Ki (> 100 µM) for the remaining 60% of the binding sites. The [3H]DA uptake experiments indicated that about 50% of uptake was SoRI-9804-sensitive. Saturation binding experiments showed that SoRI-9804 competitively inhibited [125I]RTI-55 binding to the SoRI-9804-sensitive binding component. Viewed collectively, the present results indicate that SoRI-9804 discriminates two components of the DA transporter. Further studies will be needed to determine the underlying mechanism of this effect and if partial inhibition of DA uptake results in any unique behavioral effects. Rothman, R.B., Dersch, C.M., Carroll, F.I. and Ananthan, S. Synapse, 43, pp. 268-274, 2002.

Persistent Antagonism of Methamphetamine-Induced Dopamine Release in Rats Pretreated with GBR12909 Decanoate Methamphetamine abuse is a serious global health problem and no effective pharmacological treatments have yet been developed for methamphetamine dependence. In animals, the addictive properties of methamphetamine are mediated via release of dopamine (DA) from nerve terminals in mesolimbic reward circuits. At the molecular level, methamphetamine promotes DA release by a nonexocytotic diffusion-exchange process involving DA transporter (DAT) proteins. IRP scientists have shown that blocking DAT activity with high-affinity DA uptake inhibitors, such as 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl) piperazine (GBR12909), can substantially reduce amphetamine-induced DA release in vivo. In the present study, the authors examined the ability of a long-acting depot formulation of GBR12909 decanoate (GBR-decanoate) to influence neurochemical actions of methamphetamine in the nucleus accumbens of rats. Rats received single injections of GBR-decanoate (480 mg/kg i.m.) and were subjected to in vivo microdialysis testing 1 and 2 weeks later. Pretreatment with GBR-decanoate produced modest elevations in basal extracellular levels of DA, but not 5-hydroxytryptamine (5-HT), at both time points. GBR-decanoate nearly eliminated the DA-releasing ability of methamphetamine (0.3 and 1.0 mg/kg i.v.) for 2 weeks, whereas methamphetamine-induced 5-HT release was unaffected. Autoradiographic analysis revealed that GBR-decanoate caused long-term decreases in DAT binding in the brain. These data suggest that GBR-decanoate, or similar agents, may be useful adjuncts in treating methamphetamine dependence. This therapeutic strategy would be especially useful for noncompliant patient populations. Baumann, M.H, Ayestas, M.A., Sharpe, L.G., Lewis, D.B., Rice, K.C. and Rothman, R.B., Journal of Pharmacology and Experimental Therapeutics, 301, pp. 1190-1197, 2002.

Medicinal Chemistry Section, Medications Discovery Research Branch

Enantioselective Synthesis of Novel Probes for the Dopamine Transporter Extensive structure-activity relationships at the dopamine transporter (DAT) have been developed around two classes of tropane-based ligands. Significant chemical modification at the 2-position in the 3-aryltropane (cocaine) class is well tolerated at the DAT, although optimal binding affinity results from the 2-substituent being 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 stereoselectivity suggests that these tropane-based DAT inhibitors may not access identical binding domains. In order to further investigate this hypothesis, synthesis of a series of pure S-(+)-2b-carboalkoxy-3a-[bis(4-fluorophenyl) methoxy]tropanes (>99% ee) was achieved by employing a chiral amine-induced asymmetric reaction of tropinone with methyl cyanoformate as the key step. In this series, all of the S-(+)-enantiomers were 2-fold more potent than their racemic mixtures and all displayed high affinity binding for DAT (Ki=13-40 nM). These data support previous findings of significant divergence in structural requirements for high affinity DAT binding among tropane-based inhibitors. Furthermore, the 2-substituent in the 3a-[bis(4-fluorophenyl)methoxy] tropane series is well tolerated at the DAT but not at SERT (Ki=690-2040 nM), or muscarinic M1 receptors (Ki=133-4380 nM) resulting in highly selective DAT ligands that may provide new leads toward a cocaine-abuse therapeutic. Zou, M-F., Agoston, G.E., Belov, Y., Kopajtic, T., Katz, J.L., and Newman, A.H. Bioorganic Medicinal Chemistry Letters, 12, pp. 1249-1252, 2002.

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

Cognitive Measures in Long-term Cannabis Users The cognitive effects of long-term cannabis use are insufficiently understood. Most studies concur that cognitive deficits persist at least several days after stopping heavy cannabis use. But studies differ on whether such deficits persist long-term, or whether deficits are correlated with increasing duration of lifetime cannabis use. IRP scientists administered neuropsychological tests to 77 current heavy cannabis users who had smoked cannabis at least 5000 times in their lives, and to 87 control subjects who had smoked no more than 50 times in their lives. The heavy smokers showed deficits on memory of word lists on Days 0, 1, and 7 of a supervised abstinence period. By Day 28, however, very few significant differences were found between users and controls on any test, and the authors found no significant associations between total lifetime cannabis consumption and test performance. Although these findings may be affected by residual confounding, as in all retrospective studies, they suggest that cannabis-associated cognitive deficits are reversible and related to recent cannabis exposure, rather than irreversible and related to cumulative lifetime use. Pope, H.G. Jr., Gruber, A.J., Hudson, J.I., Huestis, M.A., and Yurgelun-Todd, D. Journal of Clinical Pharmacology, 42, pp. 41S-47S, 2002.

Urinary Elimination of Cocaine Metabolites in Chronic Cocaine Users During Cessation In an earlier study, IRP scientists showed that chronic cocaine use by active illicit users produced a longer plasma half-life than expected based on acute low-dose cocaine studies. This study reports urinary excretion patterns of cocaine metabolites as benzoylecgonine (BE) equivalents from 18 of the same individuals, housed for up to 14 days on a closed research unit. In addition, the researchers evaluated whether creatinine normalization of BE equivalents increased mean detection time and reduced mean within-subject variability. All urine voids (N=953) were individually assayed; BE equivalents were determined semi-quantitatively by FPIA (TDx®, Abbott Laboratories, Abbott Park, IL). Compared to concentration in first void after admission, BE equivalents decreased to approximately 33%, 8%, and 4% at 24, 48, and 72 hours, respectively. Mean +/- SD (range) time to first negative specimen (BE equivalents <300 ng/mL) was 43.6 +/- 17.1 (16-66) hours. BE equivalents fluctuated considerably across successive specimens; 69% of participants tested positive at least once after testing negative, and the mean time to last positive specimen was 57.5 +/- 31.6 (11-147) hours after the first specimen. Thus, mean cocaine metabolite detection times were consistent with prolonged elimination, with 63% of participants testing positive longer than the expected 48-hour window of detection after admission to the unit. Mean time to last positive after last use of cocaine, known by self-report only, was approximately 81 +/- 34 [range 34 - 162] hours. Creatinine normalization, with the cutoff of 300 ng BE equivalents/mg creatinine, increased detection time: mean time to first negative specimen was 54.8 +/- 20.7 (20-100) hours, and mean time to last positive specimen was 88.4 +/- 51.0 (35.6-235) hours. Compared to concentration in the first void after admission, BE equivalents/creatinine decreased to approximately 56%, 6%, and 5% at 24, 48, and 72 hours. However, creatinine normalization did not reduce the fluctuation of BE equivalents across successive specimens. Thus, creatinine normalized values may be useful when the goal is to maximize the probability or duration of cocaine metabolite detection, but may be less useful in determining whether an individual has used cocaine since a previous specimen collection. Preston, K.L., Epstein, D.H., Cone, E.J., Wtsadik, A.T., Huestis, M.H. and Moolchan, E.T. Journal of Analytical Toxicology, 26, pp. 393-400, 2002.

Detection Times of Methamphetamine and Amphetamine In Urine Following Oral Administration of Methamphetamine To Humans Confirmation of a workplace drug test requires urinary methamphetamine (MAMP) and amphetamine (AMP) concentrations ³500 and 200 µg/L, respectively, but cutoffs at half those values (250/100) have been proposed. IRP researchers determined the urinary excretion of MAMP after oral ingestion and examined the effect of using lower cutoffs on detection of exposure. Subjects (n=8) ingested four 10-mg doses of MAMP•HCl daily over seven days and five of them ingested four 20-mg doses four weeks later. Subjects collected all urine specimens for two weeks. After solid phase extraction, MAMP and AMP were measured by GC/PCI-MS with dual silyl derivatization. MAMP and AMP were generally detected in the first or second void (0.7-11.3 h) collected following drug administration with concentrations of 82-1,827 and 12-180 µg/L, respectively. Peak MAMP concentrations (1,871-6,004 µg/L) following single doses occurred within 1.5-60 h. MAMP >=500 µg/L was first detected in the 1st or 2nd void (1-11 h) at 524-1,871 µg/L. Lowering the MAMP cutoff to 250 µg/L changed the initial detection time little. AMP >=200 µg/L was first detected in the 2nd-13th (7-20 h)

post-administration void. At a cutoff of 100 µg/L, AMP was first confirmed in the 2nd-8th void (4-13 h). Reducing the cutoff to 250/100 µg/L extended terminal MAMP detection by up to 24 h, increased total detection time by up to 34 h and increased the total number of positive specimens by 48%. At the lower cutoff, initial detection times are earlier, detection windows are longer and confirmation rates are increased. Elimination of the AMP requirement would increase detection rates and allow earlier detection. Oyler, J.M., Cone, E.J., Joseph, Jr., R.E., Moolchan, E.T., and Huestis, M.A. Clinical Chemistry, 48, pp. 1703-1714, 2002.

Pharmacokinetics and Pharmacodynamics Following Oral Codeine Administration The ease, non-invasiveness and safety of oral fluid collection have increased the use of this alternative matrix for drugs of abuse testing; however, few controlled drug administration data are available to aid in the interpretation of oral fluid results. Single 60 and 120 mg/70kg oral codeine doses were administered to 19 volunteers. Oral fluid and plasma were analyzed for free codeine, norcodeine, morphine and normorphine by SPE/GC-MS. Physiological and subjective effects were examined. Mean peak codeine concentrations were 214.2+/-27.6 and 474.3±77.0 mg/L in plasma and 638.4+/-64.4 and 1599.3+/-241.0 mg/L in oral fluid. Codeine S/P was relatively constant (approximately 4) from 1-12h. Mean t1/2 of codeine was 2.2±0.10h in plasma and 2.2+/-0.16h in oral fluid. Significant dose-related miosis and increases in sedation, psychotomimetic effect and "high" occurred after the high dose. Mean codeine oral fluid detection time was 21h with a 2.5 mg/L cutoff, longer than that of plasma (12 to 16h). Detection times with the proposed SAMHSA cutoff (40 mg/L) were only 7h. Norcodeine, but no morphine or normorphine, was quantitated in either matrix. The disposition of codeine over time was similar in plasma and oral fluid; however, due to high variability, oral fluid codeine concentrations did not reliably predict concurrent plasma concentrations. Oral fluid testing is a useful alternative matrix for monitoring codeine exposure with a detection window of 7 to 21h for single doses, depending upon cutoff concentration. These controlled drug administration data should aid the interpretation of oral fluid codeine results. Kim, I., Barnes, A.J., Oyler, J.M., Schepers, R., Joseph, Jr., R.E., Cone, E.J., Lafko, D., Moolchan, E.T., and Huestis, M.A. Clinical Chemistry, 48, pp. 1486-1497, 2002.

Drug Abuse's Smallest Victims: In Utero Drug Exposure The social and economic impact of drug use on our global population continues to increase leaving no geographical, social or cultural group untouched. The National Institute on Drug Abuse, in one of the few large surveys of maternal abuse, found that 5.5% of mothers reported taking an illicit substance during gestation. Accurate identification of in utero drug exposure has important implications for the care of the mother and child, but can raise difficult legal issues. Society discourages prenatal care with the infliction of harsh criminal penalties. Maternal drug use during pregnancy can be monitored with urine, sweat, oral fluid and/or hair testing. Detection of in utero drug exposure has traditionally been accomplished through urine testing; however, the window of detection is short, reflecting drug use for only a few days before delivery. Monitoring exposure through testing of alternative matrices, such as neonatal meconium and hair, offers advantages including non-invasive collection and detection earlier in gestation. There are many unresolved issues in monitoring in utero drug exposure that urgently require research. These can be divided into research to definitively differentiate drug exposed and non-drug exposed fetuses, determine the most efficient methods to routinely monitor women's drug use, and determine how these drug test results relate to neonatal and maternal outcomes. Research in this area is difficult and expensive to perform, but necessary to accurately assess drug effects on the fetus. By increasing our understanding of the physiological, biochemical and behavioral effects of gestational drug exposure, we may ultimately provide solutions for better drug prevention, treatment and a reduction in the number of drug-exposed children. Huestis, M.A. and Choo, R.E. Forensic Science International, 128, pp. 20-30, 2002.

Eclipse Can Deliver Crack The potential of Eclipse, a nicotine delivery device recently introduced by R.J. Reynolds Tobacco, to deliver crack cocaine was assessed in experiments utilizing a smoking machine. The quantity of cocaine delivered in smoke from crack cocaine inserted into the Eclipse cigarette was measured by gas chromatography-mass spectrometry. The Eclipse delivered 1.8 to 16.5% of the available cocaine. Eclipse could be used to deliver other drugs such as heroin, amphetamine or PCP, obviating the need to use easily identified drug paraphernalia. Steckley, S.L., Darwin, W.D., Huestis, M., Henningfield, J.E., and Pickworth, W.B. Nicotine and Tobacco Research, Suppl. pp. 189-190, 2002.

New Mass Spectrometry Technology Recently, a new atmospheric pressure

ionization technique, atmospheric pressure matrix-assisted laser desorption/ionization (AP MALDI), has been introduced by Laiko and coworkers. This source has been coupled to an orthogonal time-of-flight mass spectrometer and, more recently, to an ion trap mass spectrometer (ITMS). Here, IRP investigators present the current status of work involving the development of an AP MALDI source for an ITMS. In addition, the authors present recent work from their own laboratory to demonstrate the utility of this novel configuration. Moyer, S.C., Marzilli, L.A., Laiko, V.V., Doroshenko, V.M., Woods, A.S., and Cotter, R.J. Atmospheric Pressure Matrix Assisted Laser Desorption/Ionization Mass Spectrometry (AP MALDI) On a Quadrupole Ion Trap Mass Spectrometer Int J. Mass Spec. 12299, pp. 1-18, 2002.

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

Program Activities

New NIDA PAs and RFAs

On September 25, 2002, NIDA issued a Program Announcement entitled **NIDA Small Grants Program (PA-02-170)**. This announcement updates and replaces PAR-00-059, NIDA Small Grants Program, published in the NIH Guide for Contracts and Grants, February 10, 2000. NIDA provides research support of up to $50,000 per year (direct costs) for up to two years in order to conduct research relevant to any area of NIDA's programmatic mission.

On September 25, 2002, NIDA issued a Program Announcement entitled **Exploratory/ Developmental Grant Applications (R21) for NIDA (PA-02-171)**. This PA is a reissuance of PA-01-012, published in the NIH Guide for Contracts and Grants, November 6, 2000. The objective of the exploratory/developmental grant (R21) mechanism is to encourage applications from individuals who are interested in testing innovative or conceptually creative ideas that are scientifically sound and may advance the understanding of drug abuse and addiction.

On October 17, 2002, NIDA issued a Program Announcement entitled **Services Research in the National Drug Abuse Clinical Trials Network (PA-03-011)**. This PA invites applications to conduct health services research on the practice and delivery of drug treatment in the National Drug Abuse Clinical Trials Network (CTN). By encouraging the use of the existing CTN network of treatment providers and research centers as a platform for new research, this PA enhances research efforts to improve the delivery of drug abuse treatment, and translate science-based treatments into practice in community treatment settings.

On October 30, 2002, NIDA issued a Program Announcement entitled **Cutting-Edge Basic Research Awards (CEBRA) (PAR-03-017)**. The purpose of this PA is to invite applications for Cutting-Edge Basic Research Awards (CEBRA) to foster highly innovative or conceptually creative research that advances our understanding of drug abuse and addiction and how to prevent and treat them. The CEBRA is a new mechanism designed by NIDA to foster novel research approaches and represents the high priority placed by NIDA on identifying such research.

NIDA's International Program issued a Program Announcement, **International Research Collaboration on Drug Addiction (PAS-03-023)** on November 7, 2002 to support new and/or competitive continuation R01 grants for projects conducted in whole or in part outside the United States. The research must be conducted by U.S. investigators in collaboration with non-U.S.-based investigators. Either the U.S. or the non- U.S. investigator may serve as principal investigator, but the project must include significant contributions of resources (including in-kind resources) by each participant. This broad call for innovative research and applications encourages proposals in all areas of science addressing drug addiction, particularly projects which take advantage of a unique set of resources or subject populations. By supporting international collaborative research on drug abuse and addiction, NIDA will continue to generate important new information on the causes, consequences, prevention, and treatment of drug abuse and addiction and will also help address the growing problems related to illegal drug use and addiction around the world.

On September 16, 2002, NIDA issued an RFA entitled **Chronic Stress and Its Relation to Drug Abuse and Addiction (DA-03-004)**. This RFA encourages research on adaptive changes within the brain brought about by chronic stress or repeated stressors and their functional relevance to drug use, abuse, and addictive

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processes. The relationship between drugs of abuse such as cocaine and heroin, activation of the hypothalamo-pituitary-adrenal (HPA) axis, and neural substrates subserving cognitive or behavioral processes under conditions of chronic stress is complex, but studies of these relationships may provide clues as to how drugs of abuse can produce persistent changes in the brain that, in turn, modulate behavioral processes, including drug-seeking and drug-taking behavior.

On September 16, 2002, NIDA issued a Request for Applications entitled **Guidance For Behavioral Treatment Providers: Research on Knowledge and Skill Enhancement (DA-03-005)**. The purpose of this announcement is to support studies for developing and testing novel, creative approaches to clinical training and supervision that will enhance community treatment providers' knowledge and skills to administer behavioral treatments with some evidence of efficacy for drug abuse and/or interventions for HIV/AIDS risk reduction among in-treatment drug abusers. This RFA especially encourages theory-driven approaches to the development of novel training and supervision methods, i.e., approaches that apply knowledge derived from cognitive neuroscience, psychology, medical education, and other fields of science to training and supervision.

On December 9, 2002 NIDA issued a Request for Applications entitled **Improving Behavioral Health Services and Treatment For Adolescent Drug Abuse (DA-03-003)**. The purpose of this initiative is to build on recent studies of drug abuse treatment for adolescents to improve and expand the delivery of efficacious treatments to drug abusing youth. The RFA encourages research to: (1) investigate ways to broaden youth access to treatment services; (2) examine improvements in treatment delivery, including breadth, integration, and targeting of services for adolescents at different developmental stages in both their own maturation and their drug use and treatment careers; (3) develop, modify, or test behavioral treatments, or combined behavioral and pharmacological treatments, targeting adolescent drug abusers; and (4) analyze strategies for translating efficacious clinical treatments into effective community interventions.

On December 10, 2002, NIDA issued an RFA entitled **Translating Tobacco Addiction Research to Treatment (DA-03-010)**. The purpose of this RFA is to support research designed to translate knowledge about the targets, mechanisms and processes of nicotine addiction into treatments that are immediately applicable or demonstrably exportable to the treatment of tobacco addiction in humans. It is expected that the research will be conducted using laboratory studies with human volunteers, or Stage I style clinical studies.

On December 18, 2002, NIDA issued an RFA entitled **Diffusion of HIV Infection Through Sexual Risk Behaviors of Drug Users (DA-03-001)**. The purpose of this RFA is to stimulate collaborative research to further understanding of sexual transmission of HIV within and across drug-using population subgroups and to non-drug using populations. Through this RFA, NIDA invites cooperative agreement applications to participate in the Sexual Acquisition and Transmission of HIV Cooperative Agreement Program (SATH-CAP). The goal of this program is to support multi-disciplinary research that seeks to better understand the dynamic behavioral, biological and environmental processes implicated in the sexual transmission of HIV and other sexually transmitted infections (STI) among drug users and the diffusion of infections from drug using populations to non-drug using populations.

On December 19, 2002, NIDA issued an RFA entitled **Transdisciplinary Prevention Research Centers (DA-03-008)**. Through this RFA, NIDA invites exploratory center grant applications (P20) to support the development of transdisciplinary prevention research centers (TPRCs). These centers will extend the work of NIDA's National Prevention Research Initiative by creating environments in which scientists from the basic and applied/clinical disciplines can come together to develop a coherent program of transdisciplinary research. The ultimate goal of these centers is to overcome the barriers inherent in integrating cross-disciplinary concepts, methods, and findings that hold promise for the development of innovative prevention intervention questions and approaches.

On December 30, 2002, NIDA issued an RFA entitled **Immunotherapy for Addiction Treatment: SBIR/STTR Initiative (DA-03-015)**. This RFA encourages small businesses or small businesses in collaboration with research institutions, to develop effective methods for the large-scale production and clinical testing of monoclonal antibodies or vaccines as therapeutic agents for drug or nicotine addiction and/or overdose.

On January 6, 2003, NIDA issued an RFA entitled **Enhancing HIV Vaccine Efficacy**

in High-Risk Drug Users (DA-03-002). The purpose of this RFA is to determine the validity of novel approaches to address the prevention of HIV and related blood-borne and sexually transmitted infections as well as to establish and study cohorts of high-risk drug users in the context of the developing HIV vaccine.

On January 14, 2003, NIDA issued an RFA entitled **Stress and Drug Abuse: Epidemiology, Etiology, Prevention and Treatment (DA-04-001)**. The purpose of this RFA is to solicit applications for innovative research on chronic stress and drug abuse or dependence. Research is encouraged on the epidemiology, etiology, prevention and treatment of drug abuse/dependence, as it relates to either chronic stress or Post Traumatic Stress Disorder (PTSD). More specifically, research is sought to examine the relationship between chronic stress or PTSD and drug use, abuse and dependence. Also of interest is the relationship between chronic stress or PTSD and withdrawal/abstinence, remission and relapse.

PAs and RFAs Issued With Other NIH Components/Agencies

On September 17, 2002, NIDA, in collaboration with NIAAA, issued a Program Announcement entitled **Implementation of Screening and Brief Interventions for Alcohol-Related Problems (PA-02-168)**. The purpose of this announcement is to solicit research on the delivery of screening, identification, and brief intervention services for alcohol-related problems in medical and other similar service settings.

On September 25, 2002, NIDA, in conjuction with several other NIH Institutes, issued a Program Announcement entitled **Complications of Antiretroviral Therapy (PA-02-172)**. The intent of this PA is to encourage research in the fundamental biochemical or pathogenic mechanisms of the metabolic complications associated with HIV-disease and antiretroviral therapy.

On October 10, 2002, NIDA, along with numerous other NIH components, issued a Program Announcement entitled **Novel Genetic Methods to Map Functional Neuronal Circuits and Synaptic Change (PAR-03-007)**. This PA solicits applications to develop new genetic-based methods and technologies for the purpose of mapping functional neuronal circuits and synaptic changes in the mammalian nervous system. Emerging genetic and transgenic technologies can be used to single out functionally related cells or neuronal populations for analysis or intervention.

On October 31, 2002, NIDA, in conjunction with numerous other NIH components, issued a Program Announcement entitled **AIDS International Training and Research Program (PA-03-018)**. The purpose of this announcement is to invite applications from eligible institutions for innovative, collaborative training programs that would contribute to the long-term goal of building sustainable research capacity in HIV/AIDS and HIV-related conditions at developing country institutions. These research-training programs will strengthen scientific knowledge and skills to enhance prevention of and treatment and care for HIV/AIDS and HIV-related conditions in developing countries.

On November 7, 2002, NIDA and several other NIH Institutes jointly issued a Program Announcement entitled **Molecular Epidemiology of Cancers Associated with Acquired Immunodeficiency (PA-03-024)**. This PA invites grant applications for interdisciplinary studies to better understand the molecular epidemiology and role of cofactors in the etiology and pathogenesis of pre-neoplastic conditions and cancers occurring among persons infected with HIV.

On November 18, 2002, NIDA and NIAAA jointly issued a Program Announcement entitled **Pharmacotherapy to Treat the Comorbidity of Alcohol and Substance Use Disorders (PAS-03-029)**. This PA encourages research grant applications on pharmacological treatment for patients with alcohol use disorder (AUD) and a comorbid substance use disorder (SUD).

On December 3, 2002, NIDA, along with numerous other NIH components, issued a PA entitled **Institutional Mentored Research Scientist Development Award for Neuroinformatics (PAR-03-034)**. The purpose of this program announcement (PA) is to encourage and support the development of applications from U.S. educational institutions for Institutional Mentored Research Scientist Development Awards (K12). These awards are intended to provide funding for departments of institutions of higher education to foster the career development of individuals with interdisciplinary expertise bridging the fields of neuroscience and behavioral science research with that of informatics. This institutional career development program is offered to provide excellence in neuroscience informatics (neuroinformatics) research competency.

On December 3, 2002, NIDA, along with numerous other NIH components, issued a

PA entitled **The Human Brain Project (Neuroinformatics): Phase I Ð Feasibility; Phase II - Refinements, Maintenance and Integration (PAR-03-035)**. This PA replaces PAR-99-138. The purpose of this initiative is to encourage and support investigator-initiated research on neuroscience informatics (neuroinformatics). This research will lead to the development of new web-based databases, analytical tools, and knowledge management systems to foster sharing of data for all domains of neuroscience research. This program combines neuroscience and informatics (neuroinformatics) research to develop and apply advanced tools and approaches essential for efficient understanding of the structure, function and development in health and disorders of the nervous system, from the genetic to whole systems level.

On December 4, 2002, NIDA, along with numerous other NIH components, issued a PA entitled **Innovative Exploratory Studies and Technology Development in Neuroinformatics Research (R21) (PAR-03-036)**. The purpose of this PA is to encourage applications for a one-time grant award to support: innovative research directions requiring preliminary testing or development of neuroscience databases or analytical tools (neuroinformatics) research; exploration of the use of approaches and concepts new to a particular substantive area of neuroscience informatics (neuroinformatics) research; or research and development of new technologies, techniques or methods in informatics that will have a high impact upon the advancement of neuroscience research.

On December 4, 2002, NIDA, along with numerous other NIH components, issued a PA entitled, **Research Core Centers (P30) for Advanced Neuroinformatics Research (PAR-03-037)**. The purpose of this program announcement is to support shared coordinated resources that facilitate collaborative, interdisciplinary and multidisciplinary efforts in neuroscience informatics (neuroinformatics). This research effort through data sharing will create new capabilities in neuroinformatics and facilitate the solution of complex systems research.

On November 20, 2002, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement entitled **Bioengineering Research Partnerships (PAR-03-032)**. This PA invites applications for R01 awards to support Bioengineering Research Partnerships (BRPs) for basic and applied multidisciplinary research that addresses important biological or medical research problems. A BRP is a multi-disciplinary research team applying an integrative, systems approach to develop knowledge and/or methods to prevent, detect, diagnose or treat disease or to understand health and behavior. The partnership must include appropriate bioengineering or allied quantitative sciences in combination with biomedical and/or clinical investigators.

On December 10, 2002, NIDA and NIMH issued a Program Announcement entitled **Risk Factors for Psychopathology Using Existing Data Sets (PA-03-044)**. This PA encourages extensive and innovative use of existing data sets to study the development of psychopathology, including drug abuse, in order to guide the development of prevention and early intervention strategies. The aims of the PA are to mine the full potential of public use and other extant data sets to increase our knowledge of risk and protective factors for the development of psychopathology or resilience in community-based and and clinical populations and to encourage applications from new investigators to examine these research areas using state-of-the-art data analytic procedures.

On January 9, 2003, NIDA, along with numerous other NIH components, issued a Program Announcement entitled **Academic Research Enhancement Award (AREA) (PA-03-053)**. AREA funds are intended to support new "type1" and continuing "renewal" or "competing continuation" or "type 2" health related research projects proposed by faculty members of eligible schools and components of domestic institutions. The AREA will enable qualified scientists to receive support for small-scale research projects. These grants are intended to create a research opportunity for scientists and institutions otherwise unlikely to participate extensively in NIH programs to support the Nation's biomedical and behavioral research effort.

On January 16, 2003, NIDA, together with numerous other NIH Institutes, issued a Program Announcement entitled **Exploratory/Developmental (R21) Bioengineering Research Grants (EBRG) (PA-03-058)**. This PA invites applications to support innovative, high risk/high impact bioengineering research in new areas that are lacking preliminary testing or development. This research can explore approaches and concepts new to a particular substantive area; research and development of new technologies, techniques or methods; or initial research and development of data upon which significant future research may be built.

On January 16, 2003, NIDA, in conjunction with several other NIH Institutes, issued a Program Announcement entitled **Social and Demographic Studies of Race and Ethnicity in the United States (PA-03-057)**. The goal of this PA is to encourage research that will improve understanding of race and ethnicity in social science and demographic research. Demographic and and social aspects of race and ethnicity include issues related to understanding how the changing composition and conceptualization of race and ethnicity are affecting the U.S. socially, economically, and demographically.

On February 3, 2003, NIDA, in collaboration with NIAAA, issued a Program Announcement entitled **Behavioral Therapies Development Program (PA-03-066)**. This PA reaffirms NIDA's and NIAAA's continued and ongoing commitment to major programs of research on behavioral therapies and replaces in its entirety PA-99-107 published in the NIH Guide, Volume 22, No. 26 on May 25, 1999.

On October 7, 2002, NIDA, in collaboration with NIDCR, issued an RFA entitled **Translational Research in Dental Practice-Based Tobacco Control Interventions (DE-03-007)**. This RFA aims to stimulate research to: 1) develop and test interventions that translate findings from alcohol, tobacco and other drug prevention and treatment research into effective, dental practice-based tobacco control strategies, 2) translate findings from other theoretically-grounded basic or behavioral science research into effective dental practice-based tobacco control strategies, or 3) clarify processes that underlie or influence the translation of tobacco-related knowledge into clinical dental practice.

On October 10, 2002, NIDA, in conjunction with NIMH and NIA, issued an RFA entitled **HIV/AIDS and Aging: Basic and Clinical Research (MH-03-004)**. This RFA invites research grant applications to support research about older adults (greater than 50 years of age) infected with HIV. This is an age group that has been overlooked or ignored by many researchers throughout the pandemic. A major goal of this RFA is to begin a process where basic and clinical scientists from various disciplines can overcome barriers to cross-disciplinary aging research in the context of HIV disease and its treatment.

On October 15, 2002, NIDA and NIMH issued a joint RFA entitled **The Impact of Child Psychopathology and Childhood Interventions on Subsequent Drug Abuse (DA-03-007)**. The goal of this announcemnt is to stimulate both new studies and the addition of drug abuse-related measures to ongoing studies that will further understanding of the associations between certain psychiatric conditions and substance use disorders.

On October 17, 2002, NIDA, a number of other NIH components, and several other Federal agencies jointly issued an RFA entitled **International Cooperative Biodiversity Groups (ICBG) (TW-03-004)**. The unifying theme underlying the ICBG program is the concept that the discovery and development of pharmaceutical and other useful agents from natural products can, under appropriate circumstances, promote economic opportunities and enhanced research capacity in developing countries while conserving the biological resources from which these products are derived. This third RFA of the ICBG program represents a maturation of the 10-year old program and includes several changes from the previous RFAs, to now include increased emphasis on drug development and increased integration of conservation and development activities.

On October 15, 2002, NIDA and several other NIH components, collectively issued an RFA entitled **Health, Environment and Economic Development (TW-03-005)**. This RFA is intended to encourage developmental and exploratory research and research capacity-building in developing countries on topics that combine the issues of health, environment and economic development in order to improve scientific understanding of the relationships among those factors and suggest guidance for policy.

On November 4, 2002, NIDA, in conjunction with numerous other NIH components, issued an RFA entitled **Global Health Research Initiative Program for New Foreign Investigators (R01) (TW-03-006)**. This RFA is intended to promote productive re-entry of NIH-trained foreign investigators into their home countries as part of a broader program to enhance the scientific research infrastructure in developing countries, to stimulate research on a wide variety of high priority health-related issues in these countries, and to advance NIH efforts to address health issues of global import.

On November 7, 2002, NIDA, in conjunction with a number of other NIH components

and several agencies of foreign governments, issued an RFA entitled **Brain Disorders in the Developing World: Research Across the Lifespan (TW-03-007)**. This RFA solicits applications to plan and develop collaborative research and capacity building projects on brain disorders throughout life relevant to low- and middle-income nations. Applicants are expected to develop innovative, collaborative research programs that would contribute to the long-term goal of building sustainable research capacity in neurological/neurodevelopmental (including sensory, motor, cognitive and behavioral) impairment throughout life.

On January 6, 2003, NIDA, along with several other NIH Institutes, issued an RFA entitled **Hepatitis C: Natural History, Pathogenesis, Therapy and Prevention (DK-03-011)**. This RFA invites grant applications for both basic and clinical research in the areas of pathogenesis, natural history, therapy for and prevention of hepatitis C.

On January 9, 2003, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Mind-Body Interactions and Health: Research Infrastructure Program (R24) (OB-03-004)**. This RFA invites grant applications for infrastructure grants in support of research on mind-body interactions and health. "Mind-body interactions and health" refers to the relationships among cognitions, emotions, personality, social relationships, and health. Applicant institutions may request funds to support infrastructure and research designed to: (1) enhance the quality and quantity of mind-body and health research and (2) develop new research capabilities to advance mind-body and health research through innovative approaches.

On January 9, 2003, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Mind-Body Interactions and Health: Exploratory/Developmental Research Program (R21) (OB-03-005)**. This announcement invites grant applications for R21 Exploratory/Developmental Awards which are intended to support the development and demonstrate the feasibility of programs at institutions that have high potential for advancing mind-body and health research, but have not yet fully achieved the necessary resources and mechanisms to qualify for a R24 Research Infrastructure Award.

On January 9, 2003, NIDA, in collaboration with a number of other NIH components and several other Federal agencies, issued an RFA entitled **Phase II International Clinical, Operational and Health Services Research Training Awards for AIDS and Tuberculosis (Comprehensive ICOHRTA AIDS/TB) (TW-03-003)**. Through this RFA, the sponsoring agencies invite Phase I awardees to submit applications for Phase II cooperative agreements to develop comprehensive international clinical, operational, and health services research training programs. These applications should foster the development of integrated strategies to successfully implement evidence-based interventions pertinent to the global health crises created by HIV/AIDS and TB.

On January 14, 2003, NIDA and NIMH jointly issued an RFA entitled **Drug Abuse and HIV Prevention in Youth (DA-03-012)**. The major purpose of this RFA is to fill the need for theory-driven and research-based drug abuse-related HIV prevention interventions that will be effective in decreasing the incidence of HIV infection and AIDS in youth.

On January 15, 2003, NIDA, in collaboration with a number of other NIH components, issued an RFA entitled **Maintenance of Long Term Behavioral Change (OB-03-003)**. This RFA invites grant applications that: (1) examine biopsychosocial processes and test interventions designed to achieve long-term health behavior change and (2) a Resource Center to provide coordination for this set of research projects. Past research has typically focused on short-term behavioral change, yielding little information on how change, once achieved, is maintained over the long term. This RFA encourages investigators to expand on the current theoretical base of change processes and intervention models, as well as to consider new conceptualizations from basic research in the social and behavioral sciences.

Other Program Activities

As a result of previous international funding announcements, NIDA announced **FY 2002 funding for collaborative international research** through three Institute Divisions and one Center.

- DESPR: Dr. Geoffrey P. Hunt, Scientific Analysis Corporation, San Francisco, California, is investigating club drug use in San Francisco and Hong Kong; Dr. John Lochman, University of Alabama in Tuscaloosa, is

studying prevention efforts among high-risk boys in The Netherlands; Dr. Richard F. Catalano, University of Washington, Seattle, is studying the etiology of drug abuse in the United States and Australia; Dr. Leona L. Eggert, University of Washington, Seattle, is researching school-based prevention programs in Russia; and Dr. Linda B. Cottler, Washington University, St. Louis, Missouri, is investigating club drugs in the United States and Australia; Dr. Dwayne Simpson, Texas Christian University, Fort Worth, Texas, is studying transferring drug abuse treatment and assessment resources in the United States and the United Kingdom; Dr. Thomas Dishion, University of Oregon, Eugene, Oregon, along with researchers in Canada and Italy will be researching understanding and preventing adolescent drug abuse.

- DNBR: Dr. Robert C. Malenka, Stanford University, Palo Alto, California, and English scientists are studying the effects of drugs of abuse on synaptic processes in dopamine systems; Dr. Michael J. Kuhar, Emory University, Atlanta, Georgia, and colleagues in Turkey are researching the cocaine-regulated neurochemicals referred to as CART peptides; Dr. Barry E. Kosofsky, Massachusetts General Hospital, Boston, and colleagues in France are investigating cocaine-induced disturbances of mouse brain development; Dr. Victor J. Hruby, University of Arizona, Tucson, and colleagues in Russia are studying novel nonpeptide opiate ligands; and Dr. Susan G. Amara, University of Oregon Health and Science University, Portland, and Canadian researchers are investigating expression profiling of psychostimulant-regulated genes; Dr. Rosemary Booze, University of South Carolina at Columbia, and researchers from the United Kingdom are studying HIV/cocaine neurotoxicity in females.
- DTR&D: Dr. Shi-Jiang W. Li, Medical College of Wisconsin, Milwaukee, and Chinese researchers are using brain imaging to investigate the roles of the orbitofrontal cortex in cocaine abuse; Dr. Lirio S. Covey, New York State Psychiatric Institute, New York City, and colleagues in The Philippines are investigating maintenance treatment to prevent smoking relapse; and Dr. Chris-Ellyn Johanson, Wayne State University, Detroit, Michigan, and German scientists are using fMRI to investigate brain regions affected by tobacco craving. Dr. Joel Gelertner, Yale University, West Haven, Connecticut, and researchers from Thailand are studying the genetics of opioid dependence; Dr. Linda Buydens-Branchey, Veterans Administration New York Harbor Healthcare System, Brooklyn, NY, along with researchers from Belgium will be studying the effects of Buspirone in withdrawal from opiates
- CAMCODA: Dr. Holly C. Hagan, National Development and Research Institutes, New York, New York, and Bulgarian researchers are studying the etiology and prevention of blood-borne viruses in injection drug users; Dr. Richard S. Schottenfeld and Iranian researchers are investigating HIV risk reduction programs and drug abuse treatments; Dr. Mark L. Williams, University of Texas Health Science Center, Houston, and colleagues in Tanzania are testing peer-delivered HIV risk reduction programs stressing condom use among out-of-treatment crack cocaine smokers; and Dr. Xiao-Fang Yu, Johns Hopkins University, Baltimore, Maryland, and Chinese colleagues are investigating the effect of viral and host genetic factors on HIV transmission and pathogenesis.

NIDA's South African Initiative

Under NIDA's South African Initiative, 10 collaborative research projects were funded. All 10 feature collaborations between NIDA grantees in the United States and researchers in South Africa. The primary goal of NIDA's South African Initiative is to stimulate bi-national collaborative drug abuse research between the United States and Southern Africa in the areas of: Epidemiology/Early Interventions, Clinical, Prevention, Treatment or Health Services Research aimed at reducing drug abuse/addiction and its associated adverse behavioral, social, and health consequences (e.g. violence, infectious disease Ð HCV, HIV/AIDS, pulmonary diseases). The Southern African countries included within the general description of the region of Southern Africa are South Africa, Angola, Botswana, Lesotho, Malawi, Mozambique, Namibia, Swaziland, Zambia, Zimbabwe, Seychelles, Mauritius, Tanzania, and the Democratic Republic of the Congo.

CTN Update

Protocols CTN 0001 (Buprenorphine/Naloxone versus Clonidine for Inpatient Opiate

Detoxification), Protocol CTN 0002 (Buprenorphine/Naloxone versus Clonidine for Outpatient Opiate Detoxification), and Protocol CTN 0005 (Motivational Interviewing to Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse) have closed enrollment. Nearly 800 patients were randomized across 17 community treatment programs in 8 states.

Protocols CTN 0004, CTN-0006, and CTN-0007 are currently active and have enrolled over 1250 subjects in 20 community treatment programs across 9 states.

Protocol CTN 0008 (Baseline Survey) is actively collecting survey information.

Protocols CTN 0009 (Smoking Cessation Treatment With Transdermal Nicotine Replacement Therapy in Substance Abuse Rehabilitation Programs), 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 are expected to begin enrollment in January 2003.

Protocol CTN 0021(Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome for Spanish-Speaking Individuals Seeking Treatment for Substance Abuse) is in the final stages of approval before being launched in the CTN. Enrollment is expected to begin in March 2003.

Protocol CTN 0012 (Infections Screening in Substance Abuse Treatment Programs) is in the final stages of approval and will begin training for survey procedures in March 2003.

Protocols comprising a third wave are in various stages of development and review. These will be launched in the summer or fall 2003.

Five new research concepts have been approved for further development into protocols.

Three new nodes: California-Arizona Node (University of California, San Francisco); Northern New England Node (McLean Hospital); and Southwest Node (University of New Mexico), were awarded in September 2002 in response to RFA, DA-02-003.

Approval of Buprenorphine Products for the U. S. Market

On October 8, 2002 the U.S. Food and Drug Administration (FDA) approved Subutex (buprenorphine hydrochloride) and Suboxone (buprenorphine combined with naloxone) for prescription and sale in the U.S. NIDA, through a Cooperative Research and Development Agreement with Reckitt Benckiser, Inc. co-developed these products. The FDA approval of both of these products culminated a successful research and development activity for NIDA.

In addition to methadone and LAAM, buprenorphine can be used to treat dependence on heroin and other opioid-based prescription drugs. Buprenorphine is subject to less-stringent regulation than methadone or LAAM, meaning more doctors can prescribe it in more settings.

Buprenorphine is a partial opiate agonist: it blocks withdrawal and craving without producing a strong narcotic high. Naloxone is an opiate antagonist that is commonly used to treat opiate overdose. In addicted individuals it causes unpleasant withdrawal effects. It was added to buprenorphine to prevent diversion and abuse because its effects are felt most acutely when the pills are crushed for injection. In approving the medications, the FDA indicated that Subutex should be used at the beginning of treatment, while Suboxone should be used for maintenance.

Because these products are thought to have lower diversion potential than methadone and other full opiate agonist medications (such as morphine) the FDA concurred with the U.S. Drug Enforcement Administration's (DEA's) Oct. 7 decision to list both forms of buprenorphine under Schedule III of the Controlled Substances Act.

Immediately subsequent to FDA approval, the Substance Abuse and Mental Health Services Administration (SAMHSA), Department of Health and Human Services, formally announced its certification and training program for physicians who desire to prescribe buprenorphine for the treatment of opiate addiction.

New changes to existing law were enacted by the Drug Addiction Treatment Act of 2000, as contained in P.l07-273, "The Children's Health Act of 2000." These changes were enacted to allow for the possibility of treatment outside of Opiate Treatment

Programs (OTPs, sometimes referred to as "methadone" programs), and specify criteria for training of physicians who would enter this field. Physicians are required to have a minimum of eight hours of training to prescribe buprenorphine, and must obtain a waiver from SAMHSA. Physicians who are already certified as addiction specialists are "grandfathered" under the law and are exempt from the additional training requirements. Thus, those who are currently working in OTPs and dispensing methadone and/or LAAM will be able to begin using buprenorphine immediately. SAMHSA's Center for Substance Abuse Treatment will establish a national registry of physicians who have received certification. Currently, about 2,000 physicians have received training through CSAT, and over 1,000 have applied for waivers.

In order to monitor this new program the new law specifies that each physician outside an OTP setting is limited to treating 30 patients per year. Additionally, SAMHSA and the Drug Enforcement Administration will receive data on the amount of Subutex versus Suboxone that is being prescribed, as well as information on prescribing patterns that would indicate if a problem with a physician or pharmacy were occurring in violation of the law.

The combination product, Suboxone, is expected to be the dominant form prescribed as it is undesirable for parenteral (injection) abuse by opiate-dependent individuals. Because the effects of the opiate antagonist naloxone predominate when injected, NIDA expects that in addition to preventing its use via injection (a major vector for HIV, hepatitis, and tuberculosis), this product will have a relatively low street value as compared to all other forms of opiates that may be available. However, when the product is administered sublingually, as a treatment for existing opiate addiction, the FDA has determined it to be safe and efficacious.

Health Disparities Research

In FY 2002, NIDA awarded 24 supplements in response to its Administrative Supplements for Health Disparities Research announcement. The purpose of the solicitation was to give NIDA-funded researchers the opportunity to (1) recruit additional study participants, or (2) expand analyses of existing cohorts, which already have sufficient representation from various racial /ethnic populations, in order to assess patterns of drug use, effects, and potential adverse behavioral, social and health consequences, or differential treatment outcomes within and across racial/ethnic groups.

NIH Summer Internship Program (SIP) and the Minority Recruitment & Training Program (MRTP)

The NIH Summer Internship Program (SIP) and the Minority Recruitment & Training Program (MRTP) are now accepting applications for the Summer 2003. Both programs provide training opportunities for students who are interested in the scientific basis of drug abuse. In this program, students gain basic science and/or clinical laboratory experience, attend student seminars, and participate in a summer poster presentation. The goal of this program is to expose students to the realities of research, from experimental design to data analysis, interpretation and presentation. For information and an application for the SIP, go to www.training.nih.gov or contact Dr. Stephen Heishman (sheish@intra.nida.nih.gov). For an application or to receive information about the MRTP, contact Christie Brannock (cbrann@intra.nida.nih.gov)

NIDA's New and Competing Continuation Grants Awarded Since September 2002

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

Alexander, Andrew -- University of Wisconsin Madison
Structural & Functional Measures of Brain Development

Anderson, Carl M. -- Mc Lean Hospital (Belmont, MA)
High Field MRI of Stimulants In Adolescents At Risk

Baer, John S. -- University of Washington
Brief Substance Abuse Treatment For Homeless Adolescents

Bandstra, Emmalee S. -- University of Miami
Brain MRI/MRSI In Children Exposed In Utero To Cocaine

Bechara, Antoine -- University of Iowa
Cognitive and Neural Mechanisms of Substance Abuse

Belcher, Harolyn -- Kennedy Krieger Research Institute, Inc.
Children With Drug Exposure: Behavior and MRI Study

Bellair, Paul E. -- Ohio State University
Neighborhood Disadvantage, Gangs, Drugs, and Violence

Beyrer, Chris R. -- Johns Hopkins University
Risks for HIV and STIS Among Moscow Sex Workers

Bluthenthal, Ricky N. -- Rand Corporation
Community Context, Sep Operations, & HIV Risk Among IDUs

Boger, Dale L. -- Scripps Research Institute
Inhibitors of Fatty Acid Amide Hydrolase (FAAH)

Booth, Brenda M. -- University of Arkansas for Medical Sciences Little Rock
Rural Stimulant Use & Mental Health:Services & Outcomes

Booze, Rosemarie M. -- University of South Carolina at Columbia
Neurodevelopmental Basis(es) of Nicotine Sensitization

Bowen, Scott E. -- Wayne State University
Behavioral Effects of Gestational Inhalant Abuse In Rats

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

Broadhead, Robert S. -- University of Connecticut Storrs
Preventing HIV Among IDUs In Yaroslavl Russia

Brody, Arthur L. -- Brentwood Biomedical Research Institute
Treatments for Nicotine Dependence: Brain Mechanisms

Brown, Emery N. -- Massachusetts General Hospital
Dynamic Signal Processing Analyses of Neural Plasticity

Buydens-Branchey, Laure -- Narrows Institute for Biomedical Research, Inc.
Cholesterol and Fatty Acids In Cocaine Addiction Relapse

Cabral, Guy A. -- Virginia Commonwealth University
Functional Relevance of Microglial Cannabinoid Receptors

Carroll, Kathleen M. -- Yale University
Computer-Based Training In Cognitive Behavioral Therapy

Cascio, Michael -- University of Pittsburgh at Pittsburgh
Structural Studies of the Glycine Receptor

Casey, Betty J. -- Weill Medical College of Cornell University
Development of Prediction and Reward Related Circuitry

Chamberlain, Patricia -- Oregon Social Learning Center, Inc.
Preventing Health-Risking Behaviors In Delinquent Girls

Childress, Anna R. -- University of Pennsylvania
Brain Blood Flow Imaging of Cocaine Withdrawal & Craving

Chiu, Daniel T. -- University of Washington
Profiling Individual Synaptic Vesicles With Nanofluidics

Cochran, Susan D. -- University of California Los Angeles
Mental Health Disorders In A Sexual Minority Population

Colon, Hector M. -- Universidad Central Del Caribe
HIV Risks and Transitions To Injection Among Non-IDUs

Crits-Christoph, Paul -- University of Pennsylvania
Community-Friendly Manual Guided Drug Counseling

Dakof, Gayle -- University of Miami
Long-Term Outcomes of Adolescents In Drug Treatment

De Felice, Louis J. -- Vanderbilt University
Catecholamine Uptake, Micro-Fluorometry/Drug Screening

Deck, Dennis D. -- RMC Research Corporation

Impact of Financing on Outcomes of Methadone Maintenance

Detre, John A. -- University of Pennsylvania
Perfusion FMRI In Cocaine Addiction

Dewey, Stephen L. -- Brookhaven Science Assoc-Brookhaven National Laboratory
Optimizing Intensity and Duration of GVG Pharmacotherapy

Dingman, Sherry -- Marist College
Pf-L-Dopa: A MRI Tool For Developmental Neurobiology

Dishion, Thomas J. -- University of Oregon
Early Family-Centered Prevention of Drug Use Risk

Dluzen, Dean E. -- Northeastern Ohio Universities College of Medicine
Gender, Estrogen/Tamoxifen Modulation of Amphetamine

Dovichi, Norman J. -- University of Washington
Protein Mapping In Single Neurons: Cannabinoid Tolerance

Edwards, Ruth W. -- Colorado State University
Inhalant Use Among Rural Children: A Multicultural Study

Fals-Stewart, William -- State University of New York at Buffalo
Behavioral Couples Therapy for Drug Abuse

Feaster, Daniel -- University of Miami
Adherence In Recently Sober HIV+ Women: Ecosystemic Treatment

Fernandez-Sandin, Maria I. -- University of Miami
HIV and Hispanic Men: Impact of Drugs and Culture

Finlinson, H.A. -- Universidad Central Del Caribe
HIV, Drugs & Sexual Identity In Young Puerto Rican MSM

Fishbein, Diana H. -- Research Triangle Institute
Precursors, Insulators, and Consequences of Inhalant Use

Forgatch, Marion S. -- Oregon Social Learning Center, Inc.
Implementing Parent Management Training In Norway

Fox, Aaron P. -- University of Chicago
Nicotine Addiction: ACH Receptors and Secretion

Fried, Peter A. -- Carleton University
Prenatal Cannabis & Cigarette Exposure - Outcome

Friedmann, Peter D. -- Rhode Island Hospital (Providence, RI)
Continuity of Care for Drug-Addicted Offenders In RI

Frisman, Linda K. -- Connecticut State Department of Mental Health & Addiction Services
Connecticut Criminal Justice-DATS Research Initiative

Frost, William N. -- Finch University of Health Sciences/Chicago Medical School
Cellular Basis of Amphetamine-Induced Hallucinations

Fung, Ho-Leung -- State University of New York at Buffalo
Toxicokinetics and Toxicodynamics of Nitrite Inhalants

Gabrielli, John D. -- Stanford University
Development of Face Processing

Galli, Aurelio A. -- Vanderbilt University
Molecular Mechanisms of Stimulant Abuse

Gatley, Samuel J. -- Brookhaven Science Assoc-Brookhaven National Laboratory
Feto-Maternal Pharmacokinetics of Abused Inhalants

Gee, James C. -- University of Pennsylvania
Pediatric Template for Neuroimaging Data Analysis

Gerbert, Barbara -- University of California San Francisco
Positive Choice: Prevention for Positive Health

Goldsamt, Lloyd A. -- National Development & Research Institutes

Behavioral Aspects of HIV/HBV/HCV Risks In New Injectors

Gourevitch, Marc N. -- Yeshiva University
Addiction Medicine Physicians and Care For Hepatitis C

Greenfield, Shelly F. -- Mc Lean Hospital (Belmont, MA)
Recovery Group for Women With Substance Use Disorders

Gu, Howard H. -- Yale University
Mechanism of Drug Addiction

Gutstein, Howard B. -- University of Texas MD Anderson Cancer Center
From Drug Use To Addiction: Unearthing the Switches

Gyarmathy, V.A. -- National Development & Resesarch Institutes
Young Drug Users and HIV Risk In Budapest, Hungary

Hall, Sharon M. -- University of California San Francisco
Maintaining Abstinence In Chronic Cigarette Smokers

Hallfors, Denise D. -- Pacific Institute for Research and Evaluation
HIV In Young Adulthood: Pathways and Prevention

Hasselmo, Michael -- Boston University
A Spiking Model of Hippocampus for Guiding Behavior

Henggeler, Scott W. -- Medical University of South Carolina
Implementing Evidenced-Based Treatment for Youths

Heyman, Gene M. -- Mc Lean Hospital (Belmont, MA)
Individual Differences In Choice Study Predict Drug Use

Ho, Wenzhe -- Children's Hospital of Philadelphia
HCV, HIV and Opioids: Cellular Interactions

Hohmann, Andrea G. -- University of Georgia
Peripheral Cannabinoid Modulation of Pain Transmission

Holmes, Todd C. -- New York University
Transgenic Electrical Silencing of a Neural Circuit

Howard, Matthew O. -- Washington University
Neuropsychiatric Impairments In Adolescent MDMA Abusers

Howard, Matthew O. -- Washington University
Neuropsychiatric Impairment In Adolescent Inhalant Users

Huettel, Scott A. -- Duke University
Functional Neuroimaging of Executive Processing

Humfleet, Gary L. -- University of California San Francisco
LGBT Internet Based Smoking Treatment

Hurd, Yasmin L. -- Karolinska Institute
Dynorphin /Kappa Mesolimbic System In Heroin Abuse

Hwang, Dah-Ren -- New York State Psychiatric Institute
Kappa Receptor Selective PET Ligands

Inciardi, James A. -- University of Delaware
Delaware and New Jersey CJ-DATS Research Center

Irwin, Michael R. -- University of California Los Angeles
Cocaine Dependence: EEG Sleep and Cytokines

Jenkins, Bruce -- Massachusetts General Hospital
Imaging Dopamine-Mediated Neuro-Vascular Coupling

Johnson, Rolley E. -- Johns Hopkins University
Medications for Comorbid Cocaine and Alcohol Dependence

Jones, Hendree E. -- Johns Hopkins University
Recovery Housing for Pregnant Women

Jones, S.P. -- University of California San Diego
Effects of Abused Inhalants On VTA Neurons

Jordan, Thomas W. -- Victoria University of Wellington
A Proteomic Analysis of Drug Abuse

Kellam, Sheppard G. -- American Institutes for Research
Prevention Services In Schools for Early Drug Abuse Risk

Kelly, Brian C. -- Columbia University Health Sciences
Club Drug Initiation & HIV Risk of Mobile Suburban Youth

Kidorf, Michael S. -- Johns Hopkins University
Community-Based Intervention at Needle Exchange Sites

Kim, Mimi M. -- University of North Carolina Chapel Hill
Impact of Trauma on Substance Abusing Homeless Men

Kirby, Kimberly C. -- Treatment Research Institute, Inc.
Community Reinforcement Through Religious Communities

Koenig, Barbara A. -- Stanford University
Genetics of Nicotine Addiction-Examining Ethics & Policy

Kosten, Thomas R. -- Yale University
Cocaine Vaccine for Methadone Maintained Patients

Kral, Alexander H. -- University of California San Francisco
Evaluating Impact of a Resource Center for Drug Users

Kuhn, Cynthia M. -- Duke University
Gender Differences In Stimulant Action

Lai, Shenghan -- Johns Hopkins University
HIV, Cocaine & Regional Left Ventricular Dysfunction

Lang, Annie -- Indiana University Bloomington
Motivation, Sensation Seeking & Designing Effective PSAs

Laudet, Alexandre -- National Development & Research Institutes
Pathways To Long-Term Abstinence: Self-Help Processes

Letendre, Scott L. -- University of California San Diego
Neurocognitive Effects of HCV, HIV, and Drug Use

Leukefeld, Carl G. -- University of Kentucky
Central States Criminal Justice Drug Abuse Center

Lewandowski, Cathleen A. -- Wichita State University
Timing of Social Service Events on Women's Drug Recovery

Lewis, Michael -- University of Medicine & Dentistry of New Jersey Newark
Developmental Effects of Prenatal Cocaine Exposure

Lichstein, Kenneth L. -- University of Memphis
Treating Addiction To Sleep Medication

Liddle, Howard A. -- University of Miami
Brief Family-Based Therapy for Adolescent Drug Abuse

Lightfoot, Marguerita -- University of California Los Angeles
Homeless Youth's Reductions In HIV Risk Acts

Liu, Yijun -- University of Florida
Impaired Brain-Leptin Interaction In Chronic Tobacco Users

Lochman, John E. -- University of Alabama Tuscaloosa
Field Trial of Effects of the Coping Power Program

Lowy, Franklin D. -- Columbia University Health Sciences
Social Networks of S. Aureus Carriage Among Drug Users

Mach, Robert H. -- Washington University
Dopamine D3 Receptor Imaging Agents for PET and SPECT

Magura, Stephen -- National Development & Research Institutes
Trial of Self-Help Groups For Dually-Diagnosed Persons

Malison, Robert T. -- Yale University

Cocaine, Disulfiram & DBH: A Pharmacomechanistic Study

Mandal, Tarun K. -- Xavier University of Louisiana
SR Drug Delivery for the Treatment of Drug Abuse

Mantsch, John R. -- Marquette University
Stress Response and HPA Regulation In Cocaine Addiction

Margolin, Arthur -- Yale University
Spirituality Guided HIV Prevention for Drug Users

Marsch, Lisa A. -- University of Vermont
Computer-Assisted HIV Prevention for Young Drug Users

Martin, Billy R. -- Virginia Commonwealth University
Endogenous Cannabinoids and Brain/Immune Function

Mathews, William B. -- Johns Hopkins University
Development of PET Radioligands for Glutamate Receptors

McCann, Una D. -- Johns Hopkins University
PET Imaging MDMA Neurotoxicity

McClernon, Francis J. -- Duke University
Drug Cue Reactivity In Smokers: An fMRI Investigation

Mcginnis, Marilyn Y. -- Mount Sinai School of Medicine of NYU
Anabolic Androgenic Steroid Effects on Brain & Behavior

McMillan, Donald E. -- University of Arkansas Medical Sciences Little Rock
Drugs of Abuse: Chronic Interactions and Behavior

Melikian, Haley E. -- University of Massachusetts Medical School Worcester
Monoamine Transporter Phosphorylation and Trafficking

Mohamadzadeh, Mansour -- Tulane University of Louisiana
Dendritic Cell Targeted Hepatitis C Virus Immunotherapy

Montague, P. Read -- Baylor College of Medicine
Computational Substrates of Addiction and Reward

Morgenstern, Jonathan -- Mount Sinai School of Medicine of NYU
Club Drug Use and Risky Behaviors Among Men

Naylor, Magdalena R. -- University of Vermont
Chronic Pain TIVR To Prevent Prescription Drug Abuse

Neisewander, Janet L. -- Arizona State University
Limbic-Cortical Involvement In Drug Seeking

Nierenberg, Jay -- Nathan S. Kline Institute for Psychiatric Research
Brain Recovery Following Abstinence From Cocaine

Nixon, Sara J. -- University of Oklahoma Health Sciences Center
Neurocognition, Nicotine and Polysubstance Abuse

Noll, Douglas C. -- University of Michigan at Ann Arbor
Signal Recovery In Susceptibility Based Functional MRI

Novotny, Edward J. -- Yale University
NMR Studies of Brain Glutamate Turnover In Development

Owens, Douglas K. -- Stanford University
Making Better Decisions: Policy Modeling-AIDS/Drug Abuse

Pan, Ying-Xian -- Sloan-Kettering Institute for Cancer Research
Characterizing A Novel Promoter of Mouse Mor-1 Gene

Patrick, Kennerly S. -- Medical University of South Carolina
Methylphenidate-Ethanol Interaction In ADHD and Coabuse

Pentel, Paul R. -- Minneapolis Medical Research Foundation, Inc.
Vaccine Effects on Fetal Nicotine Exposure In Rats

Perkins, Kenneth A. -- University of Pittsburgh at Pittsburgh
Affect, Context, and Placebo Responses To Nicotine

Pollio, David E. -- Washington University
Homeless Drug Abusers: Testing A Spatial Use of Services

Prendergast, Michael L. -- University of California Los Angeles
The Pacific Coast Research Center of the NIDA CJ-DATS

Ridenuor, Ty A. -- Washington University
Inhalant Abuse and Dependence

Ringwalt, Christopher L. -- Pacific Institute for Research and Evaluation
Promoting Fidelity Using Remote and Onsite Support

Robinson, Leslie A. -- University of Memphis
Developing A Smoking Cessation Program For Adolescents

Ronen, Itamar -- University of Minnesota Twin Cities
Effects of Drug Use and Cessation On Monkey Brain

Schmitz, Joy M. -- University of Texas Health Sciences Center Houston
Combined Treatment for Cocaine-Alcohol Dependence

Shafer, Kimberly P. -- University of California San Francisco
Acute Hepatitis C Infection In Young Injectors

Shedlin, Michele -- National Development & Research Institutes
Drug Use and HIV Risk In Nicaragua

Silverman, Kenneth -- Johns Hopkins University
A Reinforcement-Based Therapeutic Workplace

Simpson, D.D. -- Texas Christian University
Criminal Justice Addiction Treatment In Texas (CJ-DATS)

Smalheiser, Neil R. -- University of Illinois at Chicago
RNAI-Mediated Gene Suppression In Adult Mammalian CNS

Smith, Austin G. -- University of Edinburgh
Precision Transgenesis Rats Via Embryonic Cell Lines

Snoddy, Jay R. -- University of Tennessee Knoxville
Bioinfomatics for Mouse Phenotype Analysis

Solomon, Daniel H. -- Brigham and Women's Hospital
Pain Medication Use & Risk Factors for Opioid Dependence

Sowell, Elizabeth R. -- University of California Los Angeles
Analyzing Functional and Structural MRI In FAS Children

Steketee, Jeffery D. -- University of Tennessee Health Sciences Center
Toluene as a Gateway Drug: Role of Dopamine Systems

Stenger, V.A. -- University of Pittsburgh at Pittsburgh
Pediatric fMRI Technology Development

Surratt, Hilary L. -- University of Delaware
HIV/AIDS Prevention Research In St. Croix, U.S.V.I.

Sylvestre, Diana L. -- O.A.S.I.S.
HCV Treatment of IDUs after Buprenorphine Stabilization

Tamagnan, Gilles -- Yale University
Development of PET and SPECT Ligands for Mglur5 Imaging

Tardiff, Kenneth J. -- Weill Medical College of Cornell University
Changes In Homicide and Drug Overdose In New York City

Taxman, Faye S. -- University of Maryland
Action Research To Advance Drug Treatment In the Criminal Justice System

Taylor, Jill -- Wadsworth Center
Predicting Liver Disease In HIV-HCV-Infected Women

Terhaar, Edward J. -- Gonzaga University
Prevalence of Use and Efficacy of Family Intervention

Thomas, David L. -- Johns Hopkins University

The Progression of Hepatitis C Among IDUs

Turner, R. Jay -- Florida State University
Physical Disability and Drug Use: Longitudinal Analyses

Turrigiano, Gina G. -- Brandeis University
Homeostatic Tuning of Synapses In Recurrent Networks

Walker, David D. -- Duke University
GHB Effects on Extracellular Dopamine

Walker, Diana J. -- University of Chicago
A Model of Inhalant Abuse Using Inhalant Responders

Walker, Ellen A. -- Albert Einstein Healthcare Network
Behavioral Pharmacology of Serotonin Inverse Agonists

Wall, Diana L. -- University of Georgia
Addiction Counseling: Career Paths & Professionalization

Weiss, Roger D. -- Mc Lean Hospital (Belmont, MA)
Modifying Group Therapy for Bipolar Abusers

Wexler, Harry K. -- National Development & Research Institutes
NDRI Colorado Research for CJ-DATS

Wilcox, George L. -- University of Minnesota Twin Cities
Peripheral Interactions of Opioid-Adrenergic Analgesics

Wiley, Ronald G. -- Vanderbilt University
MOR Expressing Neurons In Pain and Morphine Analgesia

Williams, Mark L. -- University of Texas Health Sciences Center Houston
Social Network of a Highly Active HIV/STD Core Group

Williamson, Celia -- University of Toledo
Typology of Street Prostitutes: Risk & Well-Being

Woods, James H. -- University of Michigan at Ann Arbor
CRH Antagonists for Treatment of Drug Abuse

Wu, Elwin -- Columbia University New York Morningside
Service Use By Men On Methadone Commiting Partner Abuse

Yen, T.S.B. -- Northern California Institute for Research & Education
Hepatitis C Virus Ns5a Protein and Lipid Droplets

Yin, Jerry C. -- Cold Spring Harbor Laboratory
Circadian Influences In Drosophila Memory Formation

Ziedonis, Douglas M. -- University of Medicine/Dentistry of NJ-RW Johnson Medical School
Modifying MET For Use With ASI Data

Zule, William A. -- Research Triangle Institute
Chronic Hepatitis Intervention Project for Drug Users

Zurier, Robert -- University of Massachusetts Medical School Worcester
Cannabinoid Acids as Anti-inflammatory Agents

Zvolensky, Michael J. -- University of Vermont
Sensitivity To Emotional Distress

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

Extramural Policy and Review Activities

Reviews

NIDA received 546 grant applications as the primary institute for this Council cycle. The Office of Extramural Affairs (OEA) arranged and managed 18 review meetings in which 220 of these were evaluated. These reviews included applications in chartered, standing review committees, applications in conflict-of-interest with standing committees, and submissions to special initiatives. In addition, OEA's Contracts Review Branch (CRB) arranged and managed three contract proposal review meetings and a concept review. CRB staff members have also been active in planning and recruiting for the 2003 NIH/NIDA Loan Repayment Program reviews. Of note, CRB has acquired the services of a new logistics support contractor, Lewis-William Conference and Logistics Management, LLC, of Silver Spring, MD.

NIDA's chartered committees consist of NIDA-E (Treatment Review Committee), NIDA-F (Health Services Review Committee), NIDA-L (Medications Development Committee), and NIDA-K (Training Committee). In addition to holding meetings of each of these committees, OEA staff held three Special Emphasis Panels to review applications in conflict with the chartered committees. Three Special Emphasis panels were constituted for reviews of program project applications, and another was held to review unsolicited center grants. OEA staff arranged and managed a review for applications submitted in response to the "Collaborative Clinical Studies in Drug Abuse" solicitation, and they also reviewed applications submitted to the "Minority Institutions' Drug Abuse Research Development Program" (MIDARP). The remaining panels were for the reviews of Behavioral Science Track for Rapid Transition-NIDA (B/START; 2 panels), Imaging Science Track for Rapid Transition (I/START), Cutting Edge Basic Research Awards (CEBRA), and Conference Grant mechanisms.

The following contract proposal reviews were held:

- NO1DA-3-8829: Analytical Chemistry Resource Center for Medications Development
- NO1DA-3-8823: Rodent and Monkey Tests of Medications Discovery Program
- NO1DA-3-1202: Logistics Support for Special Populations Research Development Seminar Series

A concept review for an initiative on diffusion of HIV infection through sexual risk behaviors of drug abusers was conducted.

Staff Training and Development

Dr. Mark Swieter, SRA, Basic Sciences Review Branch, OEA, continues to organize and host the OEA Symposium Series, NIDA's monthly forum for staff development. Notable events included a November 2002 presentation by Dr. Brent Stanfield, Deputy Director of the Center for Scientific Review; and a September 2002 presentation by Mr. Michel Desbois, former Chief, Information Resources and Management Branch, on the NIDA Extramural Projects Management System (NEPS). A "case studies/open forum" was held in December 2002.

Dr. William C. Grace, Deputy Director, OEA, participated in the OPM-sponsored residential course, "Developing and Communicating Leadership Competencies" at the Eastern Management Development Center in Shepherdstown, WV in November 2002.

Extramural Outreach

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Dr. Teri Levitin, Director, OEA, gave an invited presentation on NIDA programs and research opportunities at the September 2002 annual meeting of the Grants Resource Center of the American Association of State Colleges and Universities in Washington, D.C.

On November 8, 2002, Dr. Levitin joined Dr. Cindy Miner, Office of Science Policy and Communications, NIDA, and colleagues from NIMH and NIAAA at the International Society for Traumatic Stress Studies Annual Meeting in Baltimore to discuss NIH funding opportunities. Dr. Levitin spoke about the review process and research grant preparation.

Dr. Levitin spoke at the November 2002 Federation of Behavioral, Psychological & Cognitive Sciences Annual Meeting in Washington, D.C. on the NIH and NIDA review process and review policy.

Drs. Khursheed Asghar, Chief, Basic Sciences Review Branch; Mark Green, Chief, Clinical, Epidemiological, and Applied Sciences Review Branch; Teri Levitin, Director, OEA; and Rita Liu, Associate Director for Receipt and Referral, attended the annual meeting of the Society for Neuroscience and represented NIDA at various events.

Mr. Richard Harrison, Chief, Contracts Review Branch, gave the invocation for the Opening Ceremonies of the National American Indian & Alaska Native Heritage Month held at the Hubert Humphrey Building in Washington D. C. on November 1, 2002.

Mr. Harrison provided information and recruitment activities with an exhibit for the American Indian Science and Engineering Society Annual Meeting held in Tulsa, OK on November 8-10, 2002.

Dr. William C. Grace, Deputy Director, OEA, presented on the review process at NIDA and participated in discussions with other NIDA staff at a November 2002 workshop for the National Council of University Research Administrators.

The CTN Protocol Review Board met August 20, 2002 in Bethesda, Maryland, to discuss CTN 0012 (Characteristics of Screening, Evaluation, and Treatment of HIV/AIDS, Hepatitis C Viral Infections, and Sexually Transmitted Infections in Substance Abuse Treatment Programs), CTN 0017 (HIV and HCV Intervention in Drug Treatment Settings), CTN 0018 (HIV/STD Safer Sex Skills Groups for Men in Methadone Maintenance or Drug Free Outpatient Treatment Programs), and CTN 0019 (HIV/STD Safer Sex Skills Groups for Women in Methadone Maintenance or Drug Free Outpatient Treatment Programs).

The CTN Protocol Review Board met November 5, 2002 in Bethesda, Maryland, to discuss CTN 0016 (Patient Feedback: A Performance Improvement Study in Outpatient Addiction Treatment Settings) and CTN 0020 (Job Seekers Training for Patients with Drug Dependence).

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

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Congressional Affairs

(Prepared February 4, 2003)

FY 2003 Appropriations

The President's amended FY 2003 budget request for NIH is $27.243 billion. This includes a request for NIDA of approximately $960 million.

Since the beginning of the current fiscal year, the federal government has been operating under a series of Continuing Resolutions (CR). Before adjournment of the 107th Congress, Members agreed to a long-term CR that left federal funding at fiscal 2002 levels. Congressional leaders hoped to complete the 11 remaining fiscal 2003 spending bills quickly by combining them into an omnibus package. Although Members were unable to finish the process before the President's State of the Union Address as they had hoped, progress is nevertheless being made through an Omnibus Appropriations Bill, H.J. Res. 2.

The Senate passed a $391 billion FY 2003 spending package on January 23, 2003. House and Senate Conferees began meeting formally the week of February 3rd to determine final FY 2003 funding levels for all programs included in the Omnibus bill, which contains funding for the 11 appropriation bills that have not yet passed.

FY 2004 APPROPRIATIONS

The President released his FY 2004 budget request on February 3, 2003. The program level for the NIH is $27.893 billion, an increase of $549 million over the FY 2003 Amended President's Budget. For NIDA, the FY 2004 figure is $996 million, a 3.7 percent increase over the FY 2003 Amended President's Budget. When adjusted for one-time facilities costs in FY 2003, the total available for NIH non-biodefense research programs increases by 4.3 percent. The NIH President's Budget request to the Labor/Health and Human Services/Education Appropriations Subcommittee is $27.664 billion.

BILLS OF INTEREST - 107TH CONGRESS

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

H.R. 2215 -- P.L. 107-273 - the 21st Century Department of Justice Appropriations Authorization Act reauthorizes many programs and agencies at the Department of Justice for fiscal year (FY) 2002. In addition, there are several provisions addressing substance abuse treatment, research, and services. The bill was introduced in June 2001 by Rep. Sensenbrenner, (R-WI), and was signed into law by the President on November 2, 2002, [PL 107-273, 116 Stat. 1758. (Congressional Record p. D1124)].

Title II, Section 2203, the Drug Abuse Education, Prevention and Treatment Act of 2002, amends Section 464N of the Public Health Service Act to authorize the Director of NIDA to make grants or enter into cooperative agreements to expand the current and ongoing interdisciplinary research and clinical trials with treatment centers of the National Drug Abuse Treatment Clinical Trials Network relating to drug abuse and addiction, including biomedical, behavioral and social issues.

Section 2202, requires that not later than 180 days after the date of enactment, the President, after consultation with the Attorney General, Secretary of Health and Human Services, Secretary of Education, and other appropriate Federal officers, shall conduct a thorough review of all Federal drug and substance abuse treatment,

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prevention, education, and research programs; and make such recommendations to Congress as the President may judge necessary and expedient to streamline, consolidate, coordinate, simplify, and more effectively conduct and deliver drug and substance abuse treatment, prevention, and education. The report to Congress, which is being coordinated by the Office of National Drug Control Policy, will include a survey of all Federal drug and substance abuse treatment, prevention, education, and research programs; indicate the legal authority for each program, the amount of funding in the last 2 fiscal years for each program, and a brief description of the program; and identify authorized programs that were not funded in fiscal year 2002 or 2003.

H.R. 5005 - P.L. 107-296 - On November 25, 2002, the President signed into law H.R. 5005, the Homeland Security Act of 2002 as P.L. 107-296. This legislation will establish a new Executive Branch agency with responsibilities for information and infrastructure protection, science and technology in support of homeland security, border and transportation security, and emergency preparedness and response.

BILLS OF INTEREST - 108TH CONGRESS

S. 22 --The Senate Democratic Caucus, led by Senate Minority Leader Daschle (D-SD), introduced legislation that would authorize additional resources for drug and alcohol education, prevention and treatment programs. S. 8, "The Educational Excellence for All Learners Act of 2003" - referred to the Senate Health, Education, Labor, and Pensions Committee, would fully fund education reform, as called for in the "No Child Left Behind Act," and would increase authorized funding for the Safe and Drug Free Schools and Communities Program by $50 million to $700 million in FY 2004. S. 22, "The Justice Enhancement and Domestic Security Act of 2003" - referred to the Senate Judiciary Committee. Title V of the bill, entitled "Combating Drug and Violence Prevention," would provide funding for drug treatment and prevention programs.

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

MEETINGS, BRIEFINGS, VISITS

November 19, 2002 - At the request of Marcia Lee, minority staff to the Senate Committee on the Judiciary, Nancy Pilotte, Division of Neuroscience and Behavioral Research and Elizabeth Robertson, Division of Treatment Research and Development, NIDA, provided a briefing on the science and health effects of steroid use, particularly on children and young people. Leo Luberecki, HHS/ASL, and Mary Mayhew, OSPC, also attended.

December 4, 2002 - At the request of the Office of National Drug Control Policy, NIDA staff participated in a briefing for Congressional staff on recent findings of the evaluation of the Anti-Drug Media Campaign. The briefing was conducted by Wilson Compton, Director, DESPR, NIDA, and Westat contract staff David Macklin and Robert Orwin. Susan Martin, DESPR, accompanied Dr. Compton. Mary Mayhew, OSPC, also attended.

Dr. Frank Vocci, DTR&D, attended a press conference held by Senators Carl Levin and Orrin Hatch on October 9, 2002 to announce the approvals of buprenorphine (SUBUTEX) and buprenorphine/naloxone (SUBOXONE). Following remarks by both Senators, Dr, Vocci addressed NIDA's role in the development of the medications. Also presenting were Drs. Chris-Ellen Johanson, Herbert Kleber, Charles R. Schuster, and James Woods.

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International Activities

NIDA sponsored two international symposia at the annual meeting of the **International Society of Addiction Medicine**, October 2-5, 2002, in Reykjavik, Iceland. The session on psychopharmacological treatment for stimulant dependence was co-chaired by Drs. Frank Vocci and Ahmed Elkashef, both of DTR&D. Sessions on the NIDA Clinical Trials Network were chaired by NIDA grantee Dr. John Rotrosen, New York University School of Medicine, New York, Dr. Steven W. Gust, International Program, and by Dr. Betty Tai, CCTN. NIDA also supported participation in the meeting by three other grantees: Dr. Walter Ling, University of California, Los Angeles; Dr. Paula Riggs, University of Colorado Health Sciences Center, Denver; and Dr. George Woody, University of Pennsylvania, Philadelphia.

NIDA supported the participation by three researchers in a **conference on the use of the Addiction Severity Index (ASI) in Europe and developing countries**. The meeting was held January 20-24, 2003, in Stockholm, Sweden, and was cosponsored by Stockholm University and the Nordic Council for Alcohol and Drug Research, Helsinki, Finland, in collaboration with the European Monitoring Centre on Drugs and Drug Addiction, Lisbon, Portugal. The NIDA-supported participants were: Mr. Nadeem-Ur-Rehman, Pakistan; Mr. Muhammad Ayub, Pakistan; and Dr. Luis Solis, Mexico. A 1999-2000 NIDA Hubert H. Humphrey Drug Abuse Research Fellow, Dr. Sergiy V. Dvoryak, Ukraine, presented at the conference with support from the United Nations.

The 2002-2003 **NIDA INVEST Fellows have begun their research**. Dr. Isabelle Husson, France, is investigating cocaine-induced disturbances of mouse brain development with Dr. Barry E. Kosofsky, Massachusetts General Hospital, Boston, MA. Dr. Yilang Tang, China, and Dr. Joseph F. Cubells, Yale University School of Medicine, New Haven, are investigating the association between neuronal gene polymorphisms and cocaine-induced paranoia and psychotic symptoms. Dr. Tamo Nakamura, Japan, is researching the effects of diazepam on a visual same/different task in rhesus monkeys with Dr. Anthony Wright, University of Texas at Houston Medical School. In addition to conducting post-doctoral research with a NIDA grantee at a U.S. institution, 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.

NIDA welcomed the 2002-2003 **Hubert H. Humphrey Drug Abuse Research Fellows** with an orientation program September 20, 2002. NIDA staff members who briefed the Fellows about Institute activities included: Associate Director, Dr. Timothy P. Condon; Drs. Steven W. Gust and M. Patricia Needle, International Program; Dr. Frank Vocci, DTR&D; Dr. Paul Schnur, DNBR; Dr. Jag Khalsa, CAMCODA; Dr. Bennett Fletcher, DESPR; and Dr. Ling Chin, CCTN. Four Fellows are supported by NIDA: Dr. Amit Chakrabarti, India; Dr. Winston De La Haye, Jamaica; Dr. Ye Swe Htoon, Myanmar; and Mr. Alisher Latypov, Republic of Tajikistan. NIDA sponsors the competitive, 10-month Fellowships in cooperation with the U.S. Department of State, the Institute of International Education, and The Johns Hopkins University. Through a combination of academic courses and professional experience, Fellows learn about NIDA-supported drug abuse research and the application of research to the development of prevention programs, treatment protocols, and government policy.

Mr. Antonio Maria Costa, Executive Director, United Nations Office for Drug Control and Crime Prevention visited NIDA on September 26, 2002. Accompanying Mr. Costa were Gillian Murray, Head, UNDCP External Relations Office, S. Gail Robertson, Senior

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Program Analyst, Bureau for International Narcotics and Law Enforcement, Department of State, and Chris Sandrolini, Office Director for Policy Planning and Coordination of the Bureau of International Narcotics and Law Enforcement Affairs, Department of State. Mr. Costa's interests included research on the effects of long-term use of cannabis and ATS. Meeting with Mr. Costa from NIDA were Dr. Timothy P. Condon, Associate Director, NIDA, Drs. Jag Khalsa, CAMCODA, David Shurtleff, DNBR, Cindy Miner, OSPC, Patricia Needle, OSPC, and Ms. Dale Weiss, OSPC.

On September 17, 2002, a meeting was held at NIDA with five visitors from Central Asia. The Phelps Stokes Fund on behalf of the Department of State sponsored the visitors. Their visit to NIDA was part of a three-week program in the United States on Drug Education and Rehabilitation for Youth. Speaking to the group from NIDA were Drs. Jackie Kaftarian and Eve Reider, DESPR, Dr. Donald Vereen, OD, and Mr. Brian Marquis and Ms. Blair Gately, OSPC. The visitors included Mr. Issaak Dvorkin, Kazakhstan, Ms. Bahar Annanepesova, Ms. Gulistan Yazkuliyeva and Ms. Sona Chuli-Kuli, Turkmenistan, and Mr. Dmitriy Adisman, Uzbekistan.

On January 28, 2003, NIDA hosted a visit from the European Drug Demand Reduction Group. This group was visiting the United States as part of a project of the Bureau for International Narcotics and Law Enforcement Affairs, U.S. Department of State. Visitors included: Dr. Frank Pietsch, National Drug Coordinator of the Republic of Austria, Ms. Alice Schogger Consultant, Austrian Federal Ministry of Social Security and Generations, from the European Commission Mr. Timo Jetsu, Administrator, Directorate of Justice and Home Affairs, Anti-Drug Coordination Unit, from Greece, Dr. Anna Kokkevi, President, Organization for Combating Narcotics, from Italy, Mr. Pietro Soggiu Commissioner for Anti-Drug Policy for the Italian Government and Ms. Maryse Nadin, Ministry of Foreign Affairs, from The Netherlands Mr. Victor Everhardt, Senior Drug Policy Advisor, from Spain, Ms. Anna Maria Andres Ballesteros, Area Chief for International Relations, Spanish Narcotics Plan Office, from the United Kingdom, Ms. Sarah Clein, Young Peoples Drugs Policy Head and from the U.S. Department of State, Ms. Rebecca Brown Thompson, Escort Officer. Speaking to the group from NIDA were: Richard A. Millstein, Deputy Director, NIDA, Steve Gust, Ph.D., Director, NIDA International Program, Frank Vocci, Ph.D., Director, Division of Treatment Research & Development, Helen Cesari, Center for AIDS and Other Medical Consequences of Drug Abuse, Meyer Glantz, Ph.D., Division of Epidemiology, Services and Prevention Research, and David Shurtleff, Ph.D., Acting Director, Division of Neuroscience and Behavioral Research.

On October 15, 2002, Ms. Dale Weiss, International Program, OSPC, attended a Roundtable and Briefing for Congressional Staff. The American Iranian Council organized the Roundtable and Briefing. The sponsor of the meeting was Senator Chuck Hagel (R-Nebraska). The purpose of the roundtable and briefing were to describe the close relationship between drug use and HIV/AIDS in Iran, government and medical efforts to treat and combat HIV/AIDS, as well as areas of opportunity for U.S.-Iran engagement on tackling this public health and security emergency. Speakers included Professor Kaveh Khoshnood, Department of Epidemiology and Public Health, Yale University School of Medicine, and Dr. Robert G. Newman, Director, Baron Edmond de Rothschild Chemical Dependency Institute of Beth Israel Medical Center.

A "Community Connections" Public Health Group from Amur Region, Russia, sponsored by the Bureau of Educational and Cultural Exchange, U.S. Department of State visited NIDA on November 21, 2002. Drs. Tom Kresina, CAMCODA, and Patricia Needle, OSPC, presented information on Prevention and Treatment of HIV and HCV Among Injection Drug Users.

On December 17, 2002, Drs. Eve Reider, DESPR, Steve Gust and Pat Needle, OSPC/International met with Jeff Lee, Program Manager, Mentor Foundation, and Dr. Ken Winters, University of Minnesota to discuss cooperation between the Mentor Foundation and NIDA on development of global prevention awareness.

Dr. William Corrigall, DNBR, was a discussant at the 3rd International Conference on Smokeless Tobacco in Stockholm Sweden, September 22-25, 2002.

Dr. William Corrigall chaired the Tobacco Addiction panel and presented a paper on the mechanisms of nicotine addiction at a meeting of the Royal Society of Canada in Ottawa, Canada, November 23, 2002.

Dr. Frank Vocci and Mr. Jim Glass, both of DTR&D, were joined by Dr. Walter Ling at a meeting in Thailand to commemorate National Mental Health Week. The meeting was held on November 2-3, 2002 in Chiang Mai and opened by Her Royal Highness,

Princess Urolbatana. Dr. Vocci spoke on Methamphetamine Dependence and Its Pharmacotherapy Development. Dr. Ling spoke on behavioral therapies and the possible role of medications in the treatment of methamphetamine addiction. Dr. Vocci and Mr. Glass also visited data transmission facilities, held meetings with the Thai Ministry of Public Health, the CDC, academic investigators, and briefed the U.S. Ambassador on NIDA activities in Thailand.

Dr. Elizabeth Robertson, DESPR, made a presentation entitled, Re-conceptualizing Prevention Research, at the Addictions 2002 meeting held by the Elsevier Science, Inc. on September 17-19, 2002 in Eindhoven, the Netherlands.

Dr. Marilyn Huestis, IRP, recently visited England to meet with Professor David Cowan of King's College London and the Director of the Drug Control Centre to discuss anti-doping methods and procedures in sport. She also discussed potential collaborations with Drs. Paul Dedham and Keith Williams from the Laboratory of the Governmental Chemist. Dr. Huestis was also invited to the Royal Pharmacology Society to meet with the Chief Chemist, Dr. Anthony Moffat, and editors of Pharmaceutical Press. Dr. Huestis was asked to be on the editorial board of the new revision of Clarke's Isolation and Identification of Drugs. Further discussion of the medicinal uses of cannabinoids were pursued with Dr. Geoffrey Guy, president, and Dr. Philip Robson, clinical director, of GW Pharmaceuticals in Oxford, England.

See also Program Activities for a list of collaborative international research projects funded in FY 2002 and a description of NIDA's South African Initiative.

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Meetings/Conferences

NIDA, NCI and NIAAA, collaborated to hold a meeting entitled **Pharmacologic Approaches to Nicotine Addiction** on October 9-10, 2002. Participants were drawn from the extramural research community and NIH. The meeting took the form of a workgroup to address issues in the discovery, development and delivery of medications. Several next-steps are underway including further interaction with the research field and funding initiatives.

On November 1, 2002 at the Society for Neuroscience Annual Meeting, Drs. Christine Colvis and Rita Liu co-chaired a NIDA-sponsored symposium entitled **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 co-chaired a poster session, sponsored by Neuron and NIDA entitled **Systems Neurobiology and Drug Abuse**. This session featured 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."

On November 1, 2002 at the Society for Neuroscience Annual Meeting, Drs. Kenny Blum, Neuron and David Shurtleff, DNBR co-chaired a symposium, sponsored by Neuron and NIDA entitled **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 were 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, co-chaired a NIDA-sponsored symposium entitled **Systems Neurobiology of Drug Abuse**. Presentations focused on mechanisms of action of psychomotor stimulants (amphetamine and cocaine), cannabinoids (marijuana), nicotine, alcohol, opiates, and natural rewards (e.g. food, water). The speakers were: 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 chaired a NIDA-sponsored symposium entitled **Neuropeptides: A Role in Drug Abuse?** This symposium represented 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 were: Dr. Glen Hanson (NIDA/NIH), 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).

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On November 2, 2002, at the Society for Neuroscience Annual Meeting, Dr. Susan Volman chaired a NIDA-sponsored poster session: **Neurobiology of Drug Abuse: Cellular Mechanisms**. The session featured poster presentations related to the two Saturday NIDA symposia on "Neuropeptides: A Role in Drug Abuse?" and "Synaptic Change and Addiction."

On November 2, 2002, at the Society for Neuroscience Annual Meeting, Drs. Jonathan Pollock, DNBR and Susan Volman, DNBR co-chaired a NIDA-sponsored symposium entitled **Synaptic Change and Addiction**. The goal of this symposium was 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 were: 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, DNBR, co-chaired a NIDA-sponsored symposium entitled **Neurobiology of Relapse**. This program was 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 were 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 was 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 were also 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 co-chaired a NIDA-sponsored forum entitled **Minority Scholars: Research and Funding Opportunities at the National Institute on Drug Abuse**. The forum showcased research at various training levels (undergraduate, graduate, postgraduate, and faculty) affiliated with minority or majority institutions. The speakers were Dr. Delia Vazquez (University of Michigan Medical School) and Cassandra Baskfield (Virginia Commonwealth University). The forum was co-hosted by the University of Central Florida, Orlando, Florida.

A symposium on **Behavioral Drug Abuse Treatment Development as a Prototype for Addressing the Problems of Challenging Populations**, organized by DTR&D's Dr. Cece McNamara and Dr. Melissa Racioppo and chaired by Dr. Lisa Onken, was held on November 17, 2002 at the Annual Meeting of the Association For Advancement of Behavior Therapy in Reno, NV. The participants and the titles of their presentations included: Dr. Cece McNamara, NIDA, "Setting the Stage, An Introduction to NIDA's Stage Model for Behavioral Treatment Development Research ", Dr. Marsha Linehan, University of Washington, "From Theory to Therapy: How Dialectical Behavioral Therapy Researchers Met Stage I Therapy Development Challenges," Dr. Bruce Rounsaville, Yale University, "Illustrations of Key Stage II Research Concepts from the Yale Psychotherapy Center: Clinical Trials and Beyond," and Dr. William R. Miller, University of New Mexico, "The Missing Link: Transporting Efficacy into Practice". Dr. Steven Hayes, University of Nevado, Reno, was discussant.

A NIDA-sponsored scientific workshop entitled **Understanding the Social Epidemiology of Drug Abuse**, organized and co-chaired by Dr. Yonette Thomas, DESPR/ERB (the other co-chair was Dr. Leonard Syme, Professor of Epidemiology (Emeritus), University of California, Berkeley), was held on November 19, 2002, at the Neuroscience Center in Rockville, Maryland. Participants discussed the relevance and potential significant contribution of social epidemiology to the advancement of scientific knowledge in the field of drug abuse, as well as the challenge to encourage social epidemiologists to think more deeply about genes and gene-environment interactions and to encourage geneticists and genetic epidemiologists to think more deeply about the socio-environmental context.

The Center on AIDS and Other Medical Consequences of Drug Abuse (CAMCODA), co-sponsored a science meeting with NIDDK/NIH and the Veterans Health Administration on **Co-occurring Hepatitis C, Substance Abuse and Psychiatric Illness: Addressing the Issues and Developing Integrated Models of Care** held on

December 5 and 6, 2002 in Bethesda, MD. The majority of new and existing cases of hepatitis C are related to injection drug use, and in this population the prevalence of psychiatric co-morbidity is high. Although active drug use is often an exclusion for hepatitis C treatment, even substance abusers in long-term stable recovery may be excluded from interferon (IFN) therapy due to a history of psychiatric symptoms. Although interferon can lead to severe neuropsychiatric side effects including suicidality, the published evidence suggests that many patients with psychiatric diagnoses can be treated safely and effectively. Furthermore, there is now evidence that dually-diagnosed substance abusers with hepatitis C are able to complete interferon treatment with careful monitoring and aggressive intervention. Unfortunately, there are few programs or treatment models that that are designed to systematically manage the substance abuse and psychiatric co-morbidity of people with HCV immediately prior to and during IFN therapy. Therefore the purpose of convening this multidisciplinary panel of experts was to begin a discussion of the long range needs for the development of a multidisciplinary approach to HCV treatment in this challenging patient population.

CAMCODA was a co-sponsor along with NIDDK/NIH, and CDC of a workshop on **Management of Hepatitis C in Prisons** held January 25-26, 2003 in San Antonio, Texas. The workshop addressed the diagnosis, prevention, and treatment of hepatitis C in prisons. Topics included the identification of infected prisoners, treatment outcome, resource allocation, and translating and implementing recommendations into practice.

NIDA's Center on AIDS and Other Medical Consequences of Drug Abuse (CAMCODA) held a Working Meeting on **HIV Acquisition and Transmission Among Drug-Using Populations: Future Research Strategies** on October 10-11, 2002, in Washington, D.C. The meeting brought together a diverse group of experts in the HIV/AIDS behavioral research arena to discuss the status of knowledge in their respective disciplines and to exchange information and ideas on future behavioral research issues, needs, and priorities. The focus of the meeting was on what is known, and what remains unknown, about the epidemiology and prevention of sexual HIV transmission among injecting and non-injecting drug users and from drug users to non-drug-using populations. Discussion sessions provided the participants with an opportunity to ask questions and consider critical next steps in research on the behavioral, biological, and environmental processes implicated in the sexual transmission of HIV among drug-using populations. The presentations and discussions of the participants are now being prepared as manuscripts for publication in a special issue of a peer-reviewed journal, expected to be available in the spring/summer of 2003. Jacques Normand, Ph.D., and Elizabeth Lambert, M.Sc., of CAMCODA's Population-Based Health Intervention Unit, organized the Working Meeting, which was chaired by David Vlahov, Ph.D., Director of the Center for Urban Epidemiologic Studies at the New York Academy of Medicine.

NIDA's Child and Adolescent Workgroup, Street Youth Interest Group, and Center on AIDS and Other Medical Consequences of Drug Abuse (CAMCODA) sponsored a workshop on **Future Research on Runaway, Homeless, and Street Youth**, December 4, 2002, Washington, DC. Experts that have worked with these populations in urban and rural regions across the United States and Canada were invited to share their work and to identify methodological challenges and research gaps that remain in the field. Drs. Glen Hanson and Vince Smeriglio presented opening remarks. The workshop was organized by Jessica Campbell, Ph.D. and members of the Street Youth Interest Group, and was chaired by Les Whitbeck, Ph.D., of the University of Nebraska-Lincoln. The meeting agenda, list of participants, and a meeting summary will appear on the website soon and a publication in an academic journal is being considered.

Donald R. Vereen, Jr., M.D., M.P.H., Acting Chief, Special Populations Office and Special Assistant to the Acting Director, NIDA, along with Ana Anders, Senior Advisor on Special Populations, chaired the **Second Annual Conference of NIDA's National Hispanic Science Network on Drug Abuse** held on September 26 - 28, 2002 in Los Angeles, California. NIDA staff plenary presenters at the conference included Dr. Glen Hanson, Acting Director, Dr. Frank Vocci, Director, DTR&D, and Dr. Wilson Compton, Director, DESPR. In addition, NIDA staff Drs. Joseph Frascella, Jerry Flanzer and Ivan Montoya and Ms. Moira O'Brien participated in a grantwriting workshop.

On January 21st and 22nd, 2003, the Behavioral Treatment Development Branch hosted a meeting entitled, **Behavioral Treatment Research: Future Directions**. The meeting brought together leaders in the treatment research field to discuss how

to maximize the quality of the science and public health impact of NIDA's Behavioral Therapies Development Program.

CTN National Steering Committee Meetings were held in Bethesda, MD, October 21-23, 2002; and in Miami FL on January 27-29, 2003.

The **CTN Dissemination Subcommittee** conducted a meeting on October 20, 2002, in Bethesda, MD.

The **CTN Data Management Subcommittee** conducted a meeting on October 23-24, 2002, in Bethesda, MD.

A **CTN New Grantee Orientation Meeting** was held in Bethesda, Maryland on October 7-8, 2002, at which the attendees were provided information regarding the policies and procedures of the CTN.

CCTN Classroom Series: On November 8, 2002, NIDA CCTN and NIAAA Service Research Branch co-sponsored a seminar presented by Dr. Jon Morgenstern of Mount Sinai School of Medicine on testing the effectiveness of Cognitive-Behavior Therapy (CBT) in treating cocaine-addicted patients in community treatment programs; On December 6, 2002, Dr. Glen Hanson, NIDA's Acting Director presented "The Neurobiology of Addiction".

The **CTN Data and Safety Monitoring Board** met January 16-17, 2003, in Bethesda, Maryland.

The **CTN Quality Assurance Subcommittee** met January 30, 2002 in Miami, Florida.

Dr. Timothy P. Condon, Associate Director, NIDA, gave the Keynote presentation, "The Science of Addiction Treatment" at the State of Maryland Alcohol and Drug Abuse Administration Management Conference in Timonium, Maryland on September 25, 2002.

Dr. Timothy P. Condon presented "Addiction as a Brain Disease: Implications for Research and Practice" at the Addiction and the Brain Symposium at Stanford University Medical Center, Palo Alto, California, on October 4, 2002.

Dr. Timothy P. Condon presented "Neurobiology of Nicotine Addiction" at the 2002 National Conference on Tobacco or Health in San Francisco, California on November 20, 2002.

Dr. Jack Stein, Deputy Director, OSPC, presented "Quality Treatment for Substance Use Disorders" at the Demand Treatment! Leadership Institute I Conference in Miami Beach, Florida on October 21, 2002.

Dr. Jack Stein presented "Update on NIDA's Prescription Drug Abuse Initiative" for the National Council on Patient Information and Education in Washington, DC on October 22, 2002.

Dr. Jack Stein presented "Update on NIDA Activities" at CADCA's National Leadership Forum held in Washington, DC on October 25, 2002.

Dr. Jack Stein participated in a panel presentation on "Science to Services" at the Alcoholism & Substance Abuse Providers of New York State (ASAP) 6th Annual Conference in Syracuse, New York on October 28, 2002.

Dr. Jack Stein presented as the keynote speaker "Risks, Raves, & Research: Update on Club Drugs" at James Madison University in Harrisonburg, Virginia on November 4, 2002.

Dr. Jack Stein participated in a panel presentation on "Science to Services" at the ATTC Advisory Meeting in Washington, DC on November 5, 2002.

Dr. Jack Stein participated in a panel presentation on "Science to Services" at the CSAT/Practice Improvement Collaborative Meeting in Washington, DC on November 7, 2002.

Dr. Cindy Miner, Chief, Science Policy Branch, OSPC, organized and chaired the NIDA/NIMH Grantwriting Workshop at the annual American Academy of Child and Adolescent Psychiatry meeting in San Francisco, CA, October 25, 2002. Dr. Editha Nottelmann of NIMH and Dr. Melissa Racioppo of NIDA's Behavioral Treatment Development Branch also participated.

Dr. Cindy Miner organized and co-chaired the NIDA/AACAP Institute, "The Impact of Psychiatric Co-Morbidity on Substance Abuse in Children and Adolescents" at the annual American Academy of Child and Adolescent Psychiatry Meeting held in San Francisco, CA, October 26, 2002. Dr. Melissa Racioppo, Behavioral Treatment Development Branch discussed NIDA's efforts at developing integrated treatment models for co-morbid psychiatric and substance abuse problems.

Dr. Cindy Miner presented at the Pain Forum held in Washington, D.C., November 19, 2002 on NIDA's prescription drug abuse efforts.

Dr. Cathrine Sasek, OSPC, presented "Science Education at NIDA" at the Society For Neuroscience symposium "Funding Your Science Education Programs" on November 3, 2002 in Orlando, Florida.

Dr. Cathrine Sasek presented an overview of NIDA's new elementary school curriculum, "Brain Power, NIDA Junior Scientists," to the National Clearinghouse on Alcohol and Drug Information on December 10, 2002 in Rockville, Maryland.

Drs. Suman Rao, OSPC, and Mary Ann Stephens, CCTN, served as NIDA discussants regarding the NIDA-ATTC Collaboration at the ATTC Meeting on September 10, 2002 in Washington, D.C.

Dr. Suman Rao presented information about the NIDA-ATTC collaboration in dissemination efforts at the SAMSHA/ATTC Meeting on November 4, 2002 in Washington D.C.

Dr. Suman Rao gave the keynote talk at the Central New York Practice Research Network Conference, Strengthening Partnerships: Changing Systems Through Research and Practice, on November 21, 2002.

Dr. Rao S. Rapaka, DNBR, attended the 2002 Annual Meeting of the American Association of Pharmaceutical Scientists (AAPS), Toronto, November 10-14, 2002. He served as the Moderator and Chair for the AWARD luncheon for the Medicinal Chemistry Achievement Award. This years' award was presented to Dr. Alexandros Makriyannis. Dr. Rapaka chaired the interactive discussion following the award talk by Dr. Makriyannis.

Dr. Jerry Frankenheim, DNBR, presented at the Maryland Governor's Interagency Suicide Prevention Conference, Baltimore on "Neurobiology of MDMA ("Ecstasy," or "Despair"?), October 10, 2002. This was a Club Drugs Workgroup activity.

Dr. Herb Weingartner, DNBR, presented a talk and conducted a workshop at the national e-learning and collaborative meeting in Boston, MA on June 25-27, 2002. The title of his talk was "Building Learning and Collaborative Environments with Cognitive Neuroscience Knowledge"

Dr. William Corrigall, DNBR, chaired a NIDA symposium entitled Tobacco Addiction and its Treatment in Adolescent Cigarette Smokers at the 2002 National Conference on Tobacco or Health in San Francisco, CA, November 19-21, 2002.

Dr. William Corrigall presented a paper on Brain Pathways and Neurochemicals in Nicotine Addiction in a NIDA symposium entitled The Neurobiology of Nicotine Addiction at the 2002 National Conference on Tobacco or Health in San Francisco, CA, November 19-21, 2002.

Dr. William Corrigall, DNBR, presented testimony to the Cessation Subcommittee of the Interagency Committee on Smoking and Health at its December 3, 2002 meeting in Chicago, IL.

Dr. Jonathan Pollock, DNBR, organized a satellite symposium at the American Society of Human Genetics meeting on Funding Opportunities at NIDA through the Genetics of Addiction Vulnerability initiative. The symposium was held in Baltimore, MD in October 2002.

Dr. Frank Vocci, DTR&D, attended a meeting on Assessing Abuse Liability of CNS Drugs on October 27-29, 2002 in Bethesda, MD. Eleven professional societies and seven Federal agencies co-sponsored the meeting. Presentations on preclinical and clinical laboratory assessments, abuse liability and physical dependence in clinical trials for other indications, and epidemiological studies for the detection of actual abuse were discussed at the meeting. Experts deliberated on the status of the current ability to detect signals of abuse liability and the likelihood that these assays would have validity in the future. The presentation summaries will be published in a supplement of Drug and Alcohol Dependence.

Dr. Harold Gordon, DTR&D, attended the annual Society for Neuroscience meeting in Orlando, FL taking part in NIDA-sponsored events to present NIDA research to attendees and to minority faculty at a local university.

Dr. Joseph Frascella participated in a NIDA-sponsored workshop entitled "Future Research on Runaway, Homeless, and Street Youth," held in Washington, D.C., December 4, 2002.

Dr. Steven Grant, DTR&D, participated in a workshop on "NIH Funding Opportunities" at the annual meeting of the EEG and Clinical Neuroscience Society in Baltimore, Maryland on September 11-14, 2002.

Dr. Steven Grant served as moderator of a workshop entitled "fMRI Investigations in Neuropsychiatry: Approaches to Research Design and Analysis" at the annual meeting of the American College of Neuropsychopharmacology in San Juan, Puerto Rico, December 8-12, 2002. Participants in the workshop included Mark Potenza (Yale Univ), Godfrey Pearlson (Institute for Living), John Gore (Vanderbilt Univ), Daniel Kimberg (Univ Penn.), Michael Huerta (NIMH), Thomas Ross (NIDA IRP).

Dr. Lisa Onken, DTR&D, presented an Invited Address, "A Stage Model of Behavioral Treatment Research: Stimulating and Capitalizing on Behavioral Science" at the annual meeting of the Association for Advancement of Behavior Therapy on November 16, 2002 in Reno, NV. The address focused on both the accomplishments and obstacles faced by the behavioral treatment research field, and how NIDA's stage model of behavioral treatment research was designed to overcome some of these obstacles and maximize the impact of behavioral treatment research.

Dr. Lisa Onken provided introductory remarks at the meeting, "New Hope for Borderline Personality Disorder," December 2 & 3, 2002, Bethesda, MD.

Debra Grossman, DTR&D, participated in a workshop on human subjects and ethical issues related to treatment and research in the area of youth smoking cessation on October 16, 2002 in Chicago, IL.

Dr. Lula Beatty, Chief, Special Populations Office, presented a session on funding opportunities at NIDA at the Asian and Pacific Islander Summit on HIV/AIDS (API SHARE) on November 16, 2002 in Oakland, California.

Dr. Lula Beatty presented a session on funding opportunities at NIDA and NIH at the 8th International Meeting of the Research Centers in Minority Institutions on December 7, 2002 in Honolulu, Hawaii.

Dr. Lula Beatty attended a meeting of Historically Black Colleges and Universities interested in substance abuse research convened at Natcher Auditorium on December 5, 2002.

Dr. Donald R. Vereen, Jr., along with Ana Anders, held a research agenda development meeting with a group of Asian American and Pacific Islander (API) researchers and service providers on October 21 - 22, 2002 in Los Angeles, California.

Dr. Donald R. Vereen, Jr. delivered the keynote address at the Ninth Annual Conference on Behavior, Clinical Neuroscience, Substance Abuse and Culture in Los Angeles, California on October 23, 2002.

Dr. Donald R. Vereen, Jr. made a presentation at the Asian and Pacific Islander Summit on HIV/AIDS (API SHARE) on November 16, 2002 in Oakland, California.

Dr. Donald R. Vereen, Jr. participated in a conference entitled "The African Diaspora: Psychiatric Issues" at the Massachusetts General Hospital in Boston, Massachusetts November 17 - 21, 2002.

Dr. Donald R. Vereen, Jr. developed and participated in the workshop "Substance Abuse, Research Needs, and Southwest Pueblos in Albuquerque, New Mexico, November 25, 2002.

Ana Anders, Senior Advisor on Special Populations, represented NIDA at a planning meeting for the ATTC Hispanic Initiative convened by SAMHSA's Center for Substance Abuse Treatment on September 17 - 18, 2002 in Washington, D.C.

Ana Anders, as past-president of the NIH Hispanic Employee Organization, was a member of the planning committee that presented the Hispanic Heritage Month Program at NIH on September 19, 2002.

Ana Anders served as chairperson for planning the research track of the Latino

Behavioral Health Institute's annual conference held September 24 - 26, 2002 in Los Angeles, California. In addition, she moderated a panel at the same conference.

Ana Anders participated in SAMHSA's Center for Substance Abuse Treatment meeting on Children's Mental Health and Co-Occurring Issues, held on December 13, 2002 in Washington, D.C.

Jag H. Khalsa, Ph.D., CAMCODA, participated in a workshop at the Annual Meeting of the Asian and Pacific Islanders Association, Oakland, CA, November, 15-17, 2002, where he discussed current research on drug abuse and co-occurring infections including HIV, Hepatitis C, and others, with emphasis on minorities. The participants, young and established investigators, also learned about funding opportunities at NIDA.

Jag H. Khalsa, Ph.D. of CAMCODA co-chaired with Dr. Walter Royal of Morehouse Medical College, Atlanta, a session on: "Do Drugs of Abuse Impact on HIV Disease Progression?" at the Annual meeting of the Society of Neuroimmune Pharmacology (SNIP), October 2-5, 2002, Clear Water, Florida. A group of outstanding neuroimmunologists presented their current research on the subject and made recommendations for further research. The proceedings will be published in the Journal of Neuroimmunology.

Dr. Dionne J. Jones, CAMCODA, participated on a panel entitled "Model HIV/Substance Abuse Prevention Programs" and gave a talk on "Interventions for At Risk Minority Substance Abusing Women" at the Center on Substance Abuse Prevention, SAMHSA grantees conference, in Washington, DC on November 19, 2002.

On October 9, 2002, Dr. Elizabeth Robertson, DESPR, participated in the Purdue Pharma Scientific Advisory Board meeting to discussion prevention of prescription drug abuse.

Dr. Elizabeth Robertson made a presentation to the Duke University sponsored meeting titled, Deviant Peer Contagion, at the Riggs Library, Georgetown University, October 28 - October 29, 2002.

Dr. Elizabeth Robertson was invited by the Hormone Foundation to represent the Division of Epidemiology, Services and Prevention Research, at their discussions on Adolescent Hormone Abuse Prevention at the Monarch Hotel, Washington, DC, November 8, 2002.

Dr. Aria Crump, DESPR, gave a presentation entitled, "Prevention Research at NIDA: Lessons for Practice" at the CSAP Substance Abuse Prevention/HIV Prevention in Minority Communities Grantee meeting, Washington, D.C., Capital Hilton, November 19, 2002.

Dr. Shakeh J. Kaftarian presented a paper at the American Evaluation Association Conference on November 6th, 2002 in Crystal City, Virginia, Hyatt Regency Hotel. The paper was titled "Empowerment Evaluation in the Cycle of Prevention Research and Practice."

Dr. Susan Martin, DESPR, presented a talk entitled "The Effectiveness of Anti-Drug Media Campaigns to Address Youth Drug Abuse," at the annual meeting of the American Society of Criminology, Chicago, Illinois on November 14, 2002.

Dr. Eve Reider, DESPR, was a discussant at a symposium, "Assessment and Prevention of Risk-Taking Behaviors in High-Risk Populations," at the 2002 36th Annual Convention of the Association for Advancement of Behavior Therapy, November 15, 2002 at the Reno Hilton Hotel in Reno, Nevada.

Dr. Kevin Conway, DESPR, served as Discussant for the Neuroscience Seminar Series on Child and Adolescent Drug Abuse and Psychopathology: "Epidemiology of Child and Adolescent Drug Abuse and Psychopathology." Dr. Conway discussed presentations by Drs. Diane L. Elliott, E. Jane Costello, and Kathleen Merikangas.

Dr. Kevin Conway, Dr. Lynda Erinoff, and Mr. Arnold Mills, DESPR, presented a paper entitled "Understanding the Epidemiology, Etiology, and Consequences of Drug Abuse and Crime" at the 54th Annual Meeting of the American Society of Criminology held in Chicago, Illinois, on November 14, 2002.

Dr. Howard Chilcoat, DESPR, presented a paper entitled "Testing Causal Pathways between Drug Abuse and PTSD" as part of a symposium on traumatic stress and substance abuse at the annual meeting of the International Society for Traumatic Stress Studies in Baltimore, MD on November 8, 2002. He also presented this talk at

the Center for Substance Abuse Treatment's State Systems Program Development Conference in Washington DC on November 20, 2002.

Dr. Howard Chilcoat served as an expert panelist for the College on Problems of Drug Dependence meeting "Abuse Liability Assessment of CNS Drugs" October 28-29, 2002 in Bethesda, MD.

Dr. Marilyn Huestis, IRP, serves on the US Anti-doping Research Advisory Board, which oversees research projects and grants on new analytical methods, ethics in sport, and establishment of anti-doping policy. Each year the U.S. Anti-doping Agency has an international meeting on different aspects of anti-doping in sports. Representatives of most of the International Olympic Committee certified laboratories and from the different sporting societies, as well as experts in hematology, diagnostics, the World Anti-doping Agency and the Research Advisory Board attended this interesting congress. This meeting focused on "Oxygen Transport Enhancing Agents and Methods" and included detection of recombinant erythropoetin, darbopoetin, blood transfusions, high altitude training, blood substitutes, and establishment of normal group ranges and individual normal ranges.

Dr. Jean Lud Cadet, IRP, presented "Speed Kills: Molecular and Cellular Bases of Methamphetamine-induced Neuropathology" at the NIH Academy on November 26, 2002.

Dr. Betty Tai, Director, CCTN, gave the plenary presentation to attendees of the Association for Medical Education and Research in Substance Abuse (AMERSA) Annual National Conference in Washington, DC, on November 9, 2002. Her topic was "The NIDA CTNÐ Blending Research and Practice".

Dr. Betty Tai, along with CTN CTP representatives, Ron Jackson and Al Cohen participated in the National Treatment Outcomes Monitoring System (NTOMS) Data Users Panel Meeting in Arlington, Virginia, December 3-4, 2002.

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Media and Education Activities

Press Releases

September 27, 2002 - **NIDA and SAMHSA Enter Agreement to Expedite Transfer of Findings from Treatment Research into Clinical Practice**. The National Institute on Drug Abuse (NIDA) and the Substance Abuse and Mental Health Services Administration (SAMHSA) announced a unique intra-agency agreement to expedite the application of findings from treatment research into clinical application. The $1.5 million agreement between NIDA and SAMHSA's Center for Substance Abuse Treatment (CSAT) will help ensure that findings from NIDA's treatment research will be quickly and readily available to practitioners around the country. Coverage of this release appeared in *Workplace Substance Abuse Advisor* and *Alcoholism & Drug Abuse Weekly*.

September 27, 2002 - **Scholastic Classroom Magazines and NIDA Announce Science Education Partnership**. Scholastic, the global children's publishing and media company, and the National Institute on Drug Abuse (NIDA) have announced a two-year, school-based science education partnership designed to inform students ages 12 to 15 about the dangers of drug abuse. This national information campaign will reach more than 8.5 million teens and teachers.

October 2, 2002 - New NIDA Science Education Materials For Second and Third Graders Available Online. The National Institute on Drug Abuse (NIDA) has released a new elementary school curriculum: *"Brain Power! The NIDA Junior Scientists Program."* Available online and designed for use in second-and third-grade classrooms, *"Brain Power!"* focuses on the biological effects of drug abuse on the body and the brain. Coverage of this release appeared in *The Salt Lake Tribune, Join Together Online*, and *Alcoholism & Drug Abuse Weekly.*

October 9, 2002 - **NIDA Research and SAMHSA Physician Training Combine to Put Care for Opiate Dependence in Hands of Family Doctor**. Buprenorphine, a new medication developed through more than a decade of research supported by the National Institute on Drug Abuse (NIDA), will now become available to treat heroin and other opioid dependence through certification and training of physicians to use the medication by the Substance Abuse and Mental Health Services Administration (SAMHSA). Coverage of this release appeared in *The New York Times, Newsday, Washington Times, CBS News, Associated Press, Reuters Health, Chicago Tribune, Baltimore Sun, The Deseret News,* and *Alcoholism & Drug Abuse Weekly*.

October 31, 2002 - **NIDA Sponsors Frontiers in Addiction Research - A Series of Satellite Symposia - In Conjunction With Annual Society for Neuroscience Meeting in Orlando**. The National Institute on Drug Abuse (NIDA) sponsored a series of satellite symposia in conjunction with the 32nd Annual Meeting of the Society for Neuroscience, held in Orlando, Florida. A two-day NIDA mini convention *Frontiers in Addiction Research* a symposium *Neurobiology of Relapse* and a forum *Minority Scholars: Research Accomplishments and Funding Opportunities at the National Institute on Drug Abuse* were held during the Neuroscience 2002 conference in November.

November 4, 2002 - **NIDA NewsScan**

- Scientists Say Now is the Time to Stop Smoking
- Cocaine Use May Cause Increase in Coronary Calcium, an Indicator of Arteriosclerosis

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- Anti-depressant Bupropion May Alleviate Negative Mood Associated With Quitting Smoking
- Favorable Outcomes Linked to Treatment Compliance
- Special Supplement to Journal of Clinical Pharmacology Features Latest NIDA Research on Marijuana

As a result of NewsScan promotion, coverage appeared in *Time, Health & Medicine Week, Medical Letter on the CDC & FDA*, and *Substance Abuse Letter*.

November 5, 2002 - **NIDA NewsScan Special Issue, NIDA Funding News**

- NIDA and Other Agencies Establish Research Network to Improve Substance Abuse Treatment Services in Criminal Justice Settings
- NIDA Grants Will Improve Knowledge about Inhalant Abuse
- $4.5 Million Awarded to Create Community Drug Abuse Prevention Trials Network
- NIDA Initiative Designed to Make Substance Abuse Treatment More "Community Friendly"

As a result of NewsScan promotion, coverage appeared in *Substance Abuse Letter*, and *Alcoholism & Drug Abuse Weekly*.

November 22, 2002 - **NIDA Announces 2003 Science-based Resource Calendar for Asian Americans and Pacific Islanders**. In its ongoing initiative to raise awareness among cultural populations in the United States about the health risks of drug abuse and addiction, the National Institute on Drug Abuse (NIDA) has created a special calendar for Asian Americans and Pacific Islanders (AAPIs). With the creative recommendations of leading AAPI individuals and organizations nationwide, the rich histories of the many Asian, Native Hawaiian, and other Pacific Islander cultures are captured in each month's graphics and text selections, several of which include translations.

December 16, 2002 - **2002 Monitoring The Future Survey Shows Decrease in Use of Marijuana, Club Drugs, Cigarettes and Tobacco**. Results from the annual Monitoring the Future Survey of 8th, 10th and 12th grade students in U.S. schools indicate that use of marijuana, some club drugs, cigarettes and alcohol decreased from 2001 to 2002, according to the Department of Health and Human Services. The Monitoring the Future Survey is funded by the National Institute on Drug Abuse (NIDA), and is one of three major surveys through which the U.S. Department of Health and Human Services (HHS) monitors the nation's substance abuse patterns. Information from these surveys helps the nation to identify potential drug problem areas and ensure that resources are targeted to areas of greatest need. Coverage of this release appeared in *The New York Times, Wall Street Journal, Washington Post, Washington Times, USA Today, Associated Press, Reuters Health, CNN, CBS News, National Public Radio, Miami Herald, Bloomberg News, WebMD* and *Philadelphia Enquirer*.

ARTICLES OF INTEREST

October 2, 2002, *Contemporary Pediatrics* - "Club Drugs: Nothing to Rave About" - NIDA cited as information source.

October 27, 2002, *The New York Times* - "For Addicts, Relief May Be an Office Visit Away" - interview with Frank Vocci, PhD.

October 27, 2002, *Time* - "Is America Going to Pot?" - NIDA cited as information source.

December 16, 2002, *Time* - "Sweet as Candy Deadly as Cigarettes"- Interview with Wallace Pickworth, Ph.D.

December 17, 2002, *The New York Times* - "Teenage Drug Use Is Dropping, a Study Finds " -Interview with Glen R. Hanson, Ph.D., D.D.S.

Dr. Frank Vocci was interviewed by Mr. Brian Vastag for an article on Ibogaine which appeared in *JAMA* on December 25, 2002.

EDUCATIONAL ACTIVITIES

Scholastic, the global children's publishing and media company, and the National Institute on Drug Abuse (NIDA) have begun a two-year, school-based science education partnership designed to inform students ages 12 to 15 about the dangers of

drug abuse. This national information campaign will reach more than 8.5 million teens and teachers.

NIDA introduced a new elementary school curriculum: *"Brain Power! The NIDA Junior Scientists Program."* Available online and designed for use in second-and third-grade classrooms, *"Brain Power!"* focuses on the biological effects of drug abuse on the body and the brain.

Dr. Frank Vocci participated in the initial press conference on buprenorphine products on December 10 in Washington, D.C. Mr. Charles Curie, SAMHSA Administrator, Mr. Asa Hutchinson, DEA Administrator, Dr. Westley Clark, CSAT Director, Dr. Vocci and Mr. Odis Rivers presented at the press conference.

A CCTN training session entitled "How to Monitor Clinical Trials for GCP Compliance" that was conducted with members of the Network on August 11-12, 2002, in Seattle, Washington and was repeated again October 24-25, 2002, in Bethesda, Maryland.

EXHIBITS/CONFERENCES

November 7-10, 2002: American Indian Science and Engineering Society
November 7-10, 2002: International Society for Traumatic Stress Studies
November 9-13, 2002: American Public Health Association
November 13-16, 2002: Annual Biomedical Research Conference for Minority Students
November 19-21, 2002: National Conference on Tobacco or Health
December 12-15, 2002: American Academy of Addiction Psychiatry
January 9-11, 2003: Fourth Annual Juvenile and Family Drug Training Conference
February 11-14, 2003: Community Anti-Drug Coalition of America National Leadership Forum XIII
February 13-17, 2003: American Association for the Advancement of Sciences
February 19-22, 2003: Society for Research on Nicotine and Tobacco 9th Annual Meeting & Exposition
February 27- March 3, 2003: Council on Social Work Education

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Planned Meetings

On February 19, 2003, NIDA, in collaboration with NCI and NIAAA, will hold a 1-day meeting entitled **Smoking Cessation Pharmacotherapy: Accelerating Discovery-to-Delivery**. This meeting immediately precedes the annual meeting of the Society for Research on Nicotine and Tobacco.

NIDA will co-sponsor the Cold Spring Harbor Laboratory meeting entitled **Whole Genome Mutagenesis Strategies in the Mouse** on March 5-6, 2003.

The Club Drugs Workgroup has organized a Symposium, **"Club Drugs" Neuropharmacology: New Challenges**, to be held as part of the "Experimental Biology 2003" meeting, April 14, 2003, at the San Diego Convention Center. The speakers are Jerry Frankenheim, Ph.D. (The "Club Drugs" Present New Challenges), Bryan K. Yamamoto, Ph.D. (Neurotoxic Amphetamines), John Mendelson, M.D. (Functional Consequences of MDMA Abuse), O. Carter Snead III, M.D. (GHB Physiology and Pharmacology), Gerard J. Marek, M.D., Ph.D. (Hallucinogens: From LSD to Mescaline), and John W. Olney, M.D. (Neurotoxicity of NMDA Antagonists (Ketamine, PCP, N2O, Ethanol) in the Adult and Developing Brain).

NIDA, NINDS, NIMH, and NIAAA will co-sponsor a meeting entitled **Genes, Brain, Behavior: Before and Beyond Genomics** on April 16, 2003, on the NIH Campus, Wilson Hall, Building 1 as a satellite to celebrate the 50th anniversary of the discovery of the double helix.

NIDA plans to sponsor a workshop with the Human Proteome Organization (HuPO) that will take place in March 2003.

National CTN Steering Committee Meetings are planned for the following dates and locations: March 24-26, 2003, in Albuquerque, NM; June 20-21, 2003, in Fort Lauderdale, FL; and September 10-12, 2003, in Denver, CO.

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Publications

NIDA Publications

Epidemiologic Trends in Drug Abuse - Community Epidemiology Work Group, Volume I - June 2002
NIH Pub. No. 02-5109A
This report provides an ongoing assessment of drug abuse in major metropolitan areas of the United States with the purpose of keeping both public and private sector policymakers and researchers informed with current and accurate data.

Epidemiologic Trends in Drug Abuse - Community Epidemiology Work Group, Volume II - June 2002
NIH Pub. No. 02-5110A
This report provides an in-depth analysis of the epidemiologic trends and special reports for a limited audience made up primarily of drug abuse researchers who utilize this volume to identify potential areas for further research.

Public Health Report - Drug Use, HIV/AIDS, and Health Outcomes Among Racial and Ethnic Populations, Volume 117, Supplement 1 - 2002
NCADI #MS914
This publication, a supplement to the Public Health Reports, consists of 17 papers that were presented by researchers at a conference on Health Disparities sponsored by NIDA in April 2001. The volume is organized in three sections. The first section focuses on research examining disparities among the sampled groups; the second section consists of papers that highlight interventions that have been efficacious in their approaches to eliminating disparities. The final section consists of reviews of the literature illuminating the knowledge gaps that still exist and indicating the need of research.

NIDA INVEST Letter, Summer - Fall 2002
The lead story in this issue reports on NIDA international activities within the context of global drug use. The issue profiles NIDA Distinguished Scientist Petra Exnerova, Czech Republic; reports on the Seventh NIDA International Forum, Building International Research on Drug Abuse: Treatment Innovations; and announces the 2003 Forum, which will be held June 14 to 19, 2003, in Bal Harbour, Florida. International researchers were invited to apply for the 2003 WHO/NIDA/CPDD International Traveling Fellowships, offered in conjunction with the Forum. The 2002-2003 INVEST Research Fellows were announced, and a chart lists other international fellowship opportunities.

Meeting Summaries

7th NIDA International Forum
Building International Research on Drug Abuse: Treatment Innovations
This volume provides summaries of oral presentations, workshops, and discussion sessions; abstracts of oral and poster presentations; the agenda; and a participant list from the June 2002 meeting held in Quebec City, Canada, immediately following the Annual Scientific Meeting of the College on Problems of Drug Dependence.

NIDA NOTES

NIDA NOTES, Volume 17, Issue 4
NIH Pub. No. 03-3478

The lead article discusses a study that documents an increase in substance abuse and

found high levels of depression and posttraumatic stress disorder (PTSD) among New York City residents after the attacks of September 11, 2001.

The Director's Column by Dr. Glen R. Hanson focuses on inhalant abuseÑthe dangerous practice of inhaling fumes from a variety of widely available products to obtain an intoxicating effect. Educational efforts by NIDA and its partners in the National Inhalant Prevention Coalition have contributed to a downward trend in use here in the United States. NIDA has earmarked $2 million to expand inhalant abuse research and expects to fund studies on topics ranging from the molecular mechanisms of abuse to research based prevention and treatment approaches.

Other articles describe neurological abnormalities and cognitive impairments in chronic solvent abusers; a set of studies on women and smoking finding that smell and taste play a greater role in the smoking behavior of women than men, and that women smokers setting a quit date in the follicular phase of their menstrual cycles may suffer less severe tobacco withdrawal symptoms; FDA's approval of buprenorphine as a treatment for opiate dependence and addiction; and the prevalence of inhalant abuse, as reported in NIDA's annual Monitoring the Future survey of adolescents in grades 8, 10, and 12.

NIDA NOTES, Volume 17, Issue 3
NIH Pub. No. 03-3478

The lead article discusses the experimental compound SR141716, which may prove to be an effective treatment for marijuana addiction and other disorders. Dr. Marilyn Huestis and her colleagues at NIDA's Intramural Research Program found that the compound effectively reduced highs and changes in heart rate associated with marijuana use.

The Director's Column by Dr. Glen R. Hanson discusses drug abuse relapse and treatment and new research findings that shed light on drug-induced neurological changes that contribute to drug cravings.

Other articles discuss a study with laboratory rats that suggests another possible use for the compound SR141716: reducing the potency of cues associated with past cocaine abuse that trigger relapse; evidence in rats that prenatal exposure to MDMA (ecstasy) may result in long-term learning and memory impairments that are not attributed to the same type of damage to neurotransmitters previously seen in adults; highlights from the NIDA meeting, *Blending Clinical Practice and Research: Forging Partnerships to Enhance Drug Treatment*, that provided an important opportunity for clinicians and researchers to examine cutting-edge scientific findings about drug abuse and addiction and their application to clinical practice; and the new NIDA Research Report entitled Marijuana Abuse.

OUTREACH TO SPECIAL POPULATIONS

Based on the successful 2001 and 2002 Walking a Good Path Indian Country calendars, NIDA created and distributed a calendar for Asian American, Native Hawaiian, and other Pacific Islander (AAPI) audiences. Using photos and culturally relevant artwork, the calendar includes the latest information on the health effects of nicotine, methamphetamine, club drugs, MDMA, anabolic steroids, prescription drugs, inhalants, and marijuana.

Research Report Series- Heroin: Abuse and Addiction (Spanish)
September 2002
NIH Pub. No. 02-4165(S)
This booklet provides science-based information on the prevalence of heroin abuse, methods of use, short- and long-term effects of heroin abuse, and medical complications of chronic abuse. Describes effective treatment for heroin addiction and lists resources for more information.

Research Report Series- Nicotine Addiction (Spanish)
April 2002
NIH Pub. No. 01-4342(S)
This installment of the Research Report Series describes what nicotine is, presents current epidemiological research data regarding its use, and reports on the medical consequences of nicotine use. It also emphasizes the effects on the brain as well as current research findings about use during pregnancy, and treatment approaches.

CTN Publications

Twelve editions of the CTN Bulletin Board were distributed over the last several

months. The Bulletin Board is an electronic report on the activities of the various protocol teams and subcommittees of the CTN.

Documents entitled 'Successfully Including Women in Clinical Trials' and 'Guidelines for Referencing NIDA & CTN in Written Materials' received final NIDA approval and have been distributed throughout the CTN.

A Spanish language brochure for clinicians that detailed CTN 0021, Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome for Spanish-Speaking Individuals Seeking Treatment for Substance Abuse (METS), was approved and printed for distribution to the participating sites.

OTHER PUBLICATIONS

Assessing the Impact of Childhood Interventions on Subsequent Drug Abuse. On May 23-24, 2000, NIDA and NIMH cosponsored a conference to support the development of research on the impact of mental health treatments for childhood psychopathologies on later risk for drug abuse. Treating childhood psychopathologies is potentially an extremely powerful approach to the prevention of drug abuse among a population at very high risk for drug abuse. Based on the presentations and papers commissioned for the meeting, a set of journal articles has been published as a special issue of the *Journal of Consulting and Clinical Psychology* (2002, Vol. 70, No. 6, 1203-1306) edited by Meyer Glantz and Philip Kendall.

Kozel, N.J., Robertson, E.B., and Falkowski, C.L. The Community Epidemiology Workgroup Approach. Substance Use and Misuse, 37(5-7), pp. 783-803, 2002.

Compton, S.N., Burns, B.J., Egger, H.L., and Robertson, E. Review of the Evidence Base for Treatment of Childhood Psychopathology: Internalizing Disorders. Journal of Consulting and Clinical Psychology, 70(6), pp. 1240-1266, 2002.

Farmer, E.M.Z., Compton, S.N., Burns, B.J., and Robertson, E. Review of the Evidence Base for Treatment of Childhood Psychopathology: Externalizing Disorders. Journal of Consulting and Clinical Psychology, 70(6), pp. 1267-1302, 2002.

Papers presented during the 2001 NIDA sponsored health disparities workshop entitled Differential Drug Use, HIV/AIDS, and Related Outcomes Among Racial and Ethnic Populations: A Knowledge Assessment Workshop were published as a supplement to the Public Health Report in November 2002.

Swendsen, J.D., Conway, K.P., Rounsaville, B.J., and Merikangas, K.R. Are Personality Traits Familial Risk Factors for Substance Abuse? Results of a Controlled Family Study. American Journal of Psychiatry, 159, pp. 1760-1766, 2002.

Royal, W., Khalsa, J.H. and Francis, H. Metabolic Disorders in the Pathogenesis of Nervous System Damage in HIV-infected Drug Users, JAIDS, 31(supplement 2): S27-S93, October 2002.

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Synthesis and Evaluation of a Novel Series of 5-(2-(4-pyridinyl)vinyl)-6-chloro-3-((1-methyl-2-(S)-pyrrolidinyl)methoxy)pyridine Analogues as Potential Positron Emission Tomography Imaging Agents for Nicotinic Acetylcholine Receptors. J. Med. Chem., 45, pp. 2841-2849, 2002.

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Staff Highlights

Staff Honors and Awards

Dr. Marilyn Huestis, IRP, was elected to a three-year term as President of the International Association of Forensic Toxicologists (TIAFT) in Paris, France in August of 2002. Dr. Huestis is the first woman president of the organization and only the second American to hold this prestigious position.

Dr. Amy Newman, IRP, was invited to serve on the Editorial boards of the following Journals starting January 1, 2003: *Journal of Medicinal Chemistry, Letters in Drug Design and Discovery*, and *Current Organic Chemistry*.

Dr. Santosh Kulkarni, IRP, received an NIH FARE Travel award in December 2002.

Dr. Jonathan Katz, IRP, co-edited a special double issue of the *Psychopharmacology*, which was a Festschrift for P.B. Dews, R.T. Kelleher, and W. H. Morse.

Dr. Toni Shippenberg, IRP, was appointed Reviewing Editor (Systems Neuroscience/ Behavioral Neuroscience) for the *Journal of Neuroscience* effective January 1, 2003.

Staff Changes

Nicolette Borek, Ph.D. joined the Human Development Unit of the Center on AIDS and Other Medical Consequences of Drug Abuse (CAMCODA) in December 2002. Dr. Borek earned her doctorate in clinical psychology from The George Washington University in 1998. Her research has focused on at-risk youth, acculturation, and ethnic identity while her clinical experience included behavioral interventions for substance abuse for women and their young children and comorbid mental and drug abuse disorders. Prior to joining NIDA, Dr. Borek served as program official for the Child and Adolescent Research Program at the Center for Mental Health Research on AIDS at NIMH and worked on projects addressing youth behavior problems including "Youth Violence: A Report of the Surgeon General". Dr. Borek will focus on HIV prevention for high-risk youth, comorbid disorders, and life course research.

Howard Chilcoat, Sc.D. joined DESPR as Chief of the Epidemiology Research Branch in September 2002. Dr. Chilcoat is a psychiatric epidemiologist with a focus on the epidemiology of drug use and problems related to use. Most recently, he was an Associate Professor in the Department of Mental Hygiene at the Johns Hopkins Bloomberg School of Public Health. Dr. Chilcoat received his doctorate from Johns Hopkins in 1992 from the Department of Mental Hygiene and a Master's degree in Biostatistics in 1991. His research has been both substantive in nature, focusing on factors influencing transitions in stages of drug use, and methodological, applying new developments in biostatistics to address problems in psychiatric epidemiology.

Edith Davis joined OPRM's Grants Management Branch as a Grants Management Specialist on September 22, 2002. Before coming to NIDA Ms. Davis had been with the NIH Center for Scientific Review.

Hirsch Davis joined DTR&D's Medications Discovery and Toxicology Branch as a Psychologist in September 2002. Mr. Davis received his BA from the College of Wooster, Wooster OH (1977) and an MA in Psychology from the University of Illinois at Urbana-Champaign (1983). He worked at the Armed Forces Radiobiology Research Institute from 1985-1991, utilizing behavioral tasks to study the effects of radiation and radioprotectant drugs on performance. In 1991, he joined FDA's Division of Antiviral Drug Products, in the Center for Drug Evaluation and Research, where he

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used animal models to study behavioral effects of medications used in AIDS therapy. He performed this work in collaboration with the Uniformed Services University of the Life Sciences, where he holds an appointment as an Adjunct Instructor of Medical and Clinical Psychology. In 1998, he transferred to CDER's Division of Applied Pharmacological Research, where he continued the collaborative effort with USUHS on new projects, including correlating neural imaging of toxicities with behavioral effects of serotonergic compounds in animal models.

Cynthia F. Kleppinger, M.D. was recruited to the Center for Clinical Trials Network in September 2002. She received her Doctor of Medicine degree from the University of Missouri-Kansas City in 1979. She received her postgraduate training in Family Medicine at Southside Hospital in Bay Shore, N.Y. and is board certified by the American Board of Family Practice. She has held faculty positions with the State University of New York at Stony Brook and the Southside Hospital Family Practice program. She was an active practicing clinician in family and emergency medicine for many years, director of a nursing home, and occupational physician for a number of companies. From 1998-2002, she was a Clinical Reviewer in the Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, FDA. Her review work concentrated on the development of vaccines for bioterrorism use.

Kim Louth joined OPRM's Contracts Management Branch as a Contract Specialist on December 1, 2002. Prior to joining NIDA, Ms. Louth was with Equity Research Group in New Jersey.

Karla Moras, Ph.D. joined the Behavioral Treatment Development Branch, Division of Treatment Research & Development on September 23, 2002. Dr. Moras came from the University of Pennsylvania, and currently is president of the international Society for Psychotherapy Research (SPR). She was a recipient of the Society's Early Career Contribution Award, and previously was president of the North American Regional Chapter of the SPR. While at the University of Pennsylvania, Dr. Moras was involved in NIDA's Cocaine Collaborative Study of behavioral treatments for cocaine dependence. She also was the Principal Investigator of two NIMH grants: an Independent Scientist Award (K02) and a Treatment Development Grant (R21). The focus of her research was the refinement of efficacious treatments for comorbid unipolar depression and anxiety disorders for outpatients with medication resistant depression. Her research included treatment development to optimize the potential efficacy of combined medication and behavioral treatments for medication resistant depression. Earlier, Dr. Moras was involved in research on psychodiagnostic assessment methods, including the reliability and validity of the DSM-III-R criteria for various anxiety disorders and field studies on some anxiety disorders that were done in preparation for the DSM-IV.

Denise Pintello, Ph.D. joined the Science Policy Branch in the Office of Science Policy and Communications in September 2002 as a Health Science Administrator. She received her Ph.D. from the University of Maryland School of Social Work. Before arriving at NIDA, she worked at SAMHSA in the Center for Mental Health Services. As a Senior Research Associate at Caliber Associates in Virginia, Dr. Pintello conducted applied research and program evaluations within the fields of child welfare, domestic violence, mental health and substance abuse. Her publications have focused on the clinical treatment of intrafamilial child sexual abuse, behavioral factors associated with post-traumatic stress in women and predictors of child maltreatment recurrence.

Jordan Pulaski joined OPRM's Contracts Management Branch as a Contract Specialist on December 1, 2002. Prior to coming to NIDA, Mr. Pulaski was with the Department of Commerce.

Joni L. Rutter, Ph.D. joined NIDA's Genetics and Molecular Neurobiology Research Branch in the Division of Neuroscience and Behavioral Research on February 9, 2003 as a Health Scientist Administrator. Prior to entering graduate school, Dr. Rutter worked at Massachusetts General Hospital and Harvard Medical School in the Molecular Neurogenetics Unit where she was involved in cloning the gene for Neurofibromatosis Type-2. Dr. Rutter then earned her doctorate from the Department of Pharmacology and Toxicology at Dartmouth Medical School where she studied the transcriptional regulation of matrix-metalloproteinase-1, leading to the discovery and patent of a single nucleotide polymorphism in its promoter. Dr. Rutter's post-doctoral work at the National Cancer Institute expanded her work on genetic variation and susceptibility to complex diseases, such as breast and ovarian cancer. At NIDA, Dr. Rutter will be involved with research programs on genetic susceptibility and pharmacogenetics.

Nancy Sorrell joined the CCTN as a secretary in August 2002. Prior to joining the CCTN, Nancy was employed as an administrative secretary with Nationwide and as a legal secretary with law firms in Columbus, Ohio. Other positions she has held include employment with the National Academy of Sciences, Prince George's County Government, and Classic Corporation. Nancy received the designation of Certified Professional Secretary (CPS) in 2000 after passing the examinations administered by International Association of Administrative Professionals. Nancy has attended the University of Maryland and Columbus State Community College and has taken courses in business management and paralegal studies.

Anna Staton joined OSPC in October 2002 as a Public Health Advisor. Previously, Ms. Staton held a position at the Institute of Medicine (IOM), responsible for analyzing and evaluating data in the HIV Prevention Strategies Study, Veterans and Agent Orange Study and the E Coli Risk Assessment Study. She received a Masters in Public Administration from George Washington University. Ms. Staton will be responsible for collecting, analyzing and reporting information relating to NIDA's research programs and other Science Policy Branch programs.

Jack B. Stein, Ph.D. was recently named as Chief, Services Research Branch, DESPR. Dr. Stein served as the Deputy Director, Office of Science Policy and Communications (OSPC) since 1997. While in OSPC, Dr. Stein coordinated numerous research dissemination activities including national conferences, Town Meetings, and regional "blending" conferences, as well as the development of various publications.

Lucinda Miner, Ph.D., Chief of OSPC's Science Policy Branch has been named Acting Deputy Director, OSPC.

Kathrine Sasek, Ph.D. has been appointed Acting Chief of OSPC's Science Policy Branch.

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Grantee Honors

A Social Policy Award for Best Journal Article was presented to **Thomas J. Dishion, Ph.D.** of the University of Oregon by the Society for Research on Adolescence (SRA) at their biennial meeting in New Orleans LA in April 2002. The article, "When Interventions Harm: Peer Groups and Problem Behavior," was written with Joan McCord, Ph.D. and Francois Poulin, Ph.D. The article, which appeared in *American Psychologist*, volume 54 (1999), addressed the potential negative effects of aggregating high-risk adolescent youth into interventions or programs designed to reduce problem behavior. The article documents that negative effects may persist well into adulthood.

Dr. Peter Friedmann of Brown Medical School received the Bruce M. Selya Award for Research Excellence from Lifespan Hospitals. His research on maintenance care for alcohol problems in remission in primary care won him a semi-finalist award in a competition for the Best Abstract Award at the 26th Annual National Meeting of the Association for Medical Education and Research in Substance Abuse, November, 2002.

Dr. Lillian Gelberg, Associate Professor at the University of California Los Angeles, was appointed the George F. Keller Professor of Family Medicine. She is the first honoree of this chair, which carries a five-year appointment. Dr. Gelberg is also the first honoree to be awarded the California Academy of Family Physicians Family Practice Excellence in Research Award.

On November 5, 2002, **Dr. Merwyn "Mitch" Greenlick**, the CTN Oregon Node PI, was elected to the Oregon House of Representatives.

Ron Jackson, the CTN Washington Node CTP Representative, was selected by the American Association for the Treatment of Opiate Dependence to receive the Nyswander-Dole Award in recognition for his tireless work in support of methadone maintenance treatment.

Dr. Rolf Loeber, of the University of Pittsburgh Western Psychiatric Institute and Clinic, has been included in the roster of Highly Cited Psychologists, compiled by the Institute for Scientific Information, which publishes Science Citation Index and Social Science Citation Index. The highly-cited award is based on being in the upper 1/2 of 1% of researchers in psychology and psychiatry, in terms of citation of one's work by peers.

Dr. Alexandros Makriyannis of the University of Connecticut is the recipient of the Medicinal Chemistry Achievement Award for 2002. This award is presented every two years to an eminent scientist by the American Association of Pharmaceutical Scientists (AAPS). Dr. Alexandros Makriyannis is a NIDA grantee and has contributed substantially to the advancement of chemistry and medicinal chemistry of cannabinoids and endocannabinoids. Dr. Makriyannis presented his research on medicinal chemistry of cannabinoids at his award ceremony.

Heidi Resnick, Ph.D. of the Medical Univsrsity of South Carolina received a certificate of appreciation from the Association for the Advancement of Behavior Therapy in recognition of, and appreciation for, her valued effort and service to our country in response to the events of September 11, 2001.

Richard Rothenberg, M.D., M.P.H., Professor, Department of Family and Preventive Medicine at Emory University School of Medicine, Atlanta, GA, received the 2002 Thomas Parran Award at the 40th annual Infectious Disease Society of America meeting in Chicago, IL, on October 24, 2002. The Parran Award is the highest honor

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given by the American Sexually Transmitted Diseases Association, in recognition of lifetime career achievement in the fields of sexually transmitted diseases and HIV research. Dr. Rothenberg's award lecture addressed current complexities in STD transmission dynamics.

Dr. Michael Slater of Colorado State University was elected chair of the Coalition for Health Communication, a group representing the health communication divisions of the International Communication Association, the National Communication Association, and the American Public Health Association.

Dr. Dale Walker, a Co-PI from the CTN Oregon Node, received the American Psychiatrist Award from the National Alliance for the Mentally Ill (NAMI). In addition, he received the American Psychiatric Association's Warren Williams Award for his work with American Indians struggling with substance abuse.

Dr. Thomas Wills, of the Albert Einstein College of Medicine at Yeshiva Univerisity, has been included in the roster of Highly Cited Psychologists, compiled by the Institute for Scientific Information, which publishes Science Citation Index and Social Science Citation Index. Inclusion is based on citation in peer-reviewed journals indexed by SCI and SSCI. The highly-cited award is based on being in the upper 1/2 of 1% of researchers in psychology and psychiatry, in terms of citation of one's work by peers.

Dr. Ken Winters, Associate Professor at the University of Minnesota Twin Cities, received several honors this past year. He was selected to be associate editor of the journal *Psychology of Addictive Behaviors*, a member of the editorial board of the *Journal of Substance Abuse Treatment*, and chair of the technical advisory network for a program on international drug prevention that is supported by the Mentor Foundation.