National Institute on Drug Abuse

Director's Report

to the

National Advisory Council on Drug Abuse

February, 2000

Index

[Office of Director] [First Report Section]

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Research Findings

Basic Research

A Brain Protein Is Involved in Switching On Cocaine Addiction

Chronic exposure to cocaine causes the delta-FosB transcription factor to be expressed persistently in the nucleus accumbens. Thus, researchers hypothesized that delta-FosB may mediate some of the long-lived increases in sensitivity to the stimulant and rewarding effects of cocaine. Dr. Eric Nestler of Yale University and his colleagues tested whether delta-FosB expression actually increased the responsiveness to cocaine by generating genetically altered mice that produced large quantities of delta-FosB in the nucleus accumbens. The animals exhibited increased responsiveness to the rewarding and locomotor-activating effects of cocaine. The researchers then showed that delta-FosB increases the expression of a glutamate receptor, GluR2, in the nucleus accumbens. Indeed, overexpression of GluR2 expression in the nucleus accumbens was sufficient to account for the enhanced sensitivity to cocaine's rewarding effects seen in the mice with augmented levels of delta-FosB. The authors concluded that delta-FosB, by altering gene expression, enhances sensitivity to cocaine and may thereby contribute to cocaine addiction. This research offers insight into the nature of the switch from use to addiction, by demonstrating that sustained expression of delta-FosB is involved in the increased sensitivity to cocaine that may be related to addiction. Kelz, M.B., Chen, J., Carlezon, W.A. Jr., Whisler, K., Gilden, L., Beckmann, A.M., Steffen, C., Zhang, Y.J., Marotti, L., Self, D.W., Tkatch, T., Baranauskas, G., Surmeier, D.J., Neve, R.L., Duman, R.S., Picciotto, M.R., Nestler, E.J. Expression of the Transcription Factor Delta FosB in the Brain Controls Sensitivity to Cocaine. Nature, 401(6750), pp. 272-276, 1999.

Methamphetamine May Kill Cortical Neurons via Excessive Sensory Stimulation

Dr. John F. Marshall found that a group of pyramidal neurons located in the somatosensory cortex of the rat are killed by moderate, repeated doses of methamphetamine, in addition to the well-known injury to dopamine- and serotonin-containing terminals elsewhere in the brain. He hypothesizes that the cortical neurons die from a combination of hyperthermia and intense, prolonged excitation resulting from the rats' repetitive head and whisker movements during exposure to methamphetamine. His first experiments determined that the cortical neurons that die following a neurotoxic regimen of methamphetamine are located within the histochemically identified whisker "barrels" of the rat. The methamphetamine treatment induced Fluoro-Jade (fluorescent dye that specifically marks dying cells) positive cortical neurons only in cytochrome oxidase-stained "barrels" (discrete units containing about 2500 neurons arranged in a cylindrical array; each barrel contains the sensory representation of an individual whisker) of the somatosensory cortex. He reasons that some of the affected neurons are corticostriatal glutamatergic neurons, which, as they begin to degenerate, release excessive glutamate in the striatum, which contributes to damaging dopamine terminals in that structure. His most recent experiments demonstrated that removal of one set (left or right) of whiskers leads to reduced numbers of degenerating cortical neurons within the contralateral somatosensory cortex (consistent with the crossed projections of the whiskers). This provides evidence that the degeneration of somatosensory cortex neurons after methamphetamine depends at least in part on the stimuli arising from body movement. O'Dell, S.J. and Marshall, J.F. Effects of Vibrissae Removal on Methamphetamine-Induced Damage to Neurons in Rat Somatosensory Cortex. Society for Neuroscience, 25, Abstract 836.17, 1999.

Differential Effects of Neuropeptide Y and the Mu-Agonist DAMGO on 'Palatability' vs. 'Energy'

A variety of studies suggest that Neuropeptide Y (NPY) is an important regulator of energy metabolism. In contrast, the opioid peptides appear to influence the rewarding aspects of feeding. In this study, Dr. Levine and his research team stimulated feeding by injecting NPY or the mu-opioid agonist DAMGO into the paraventricular nucleus of rats. Following injection, rats were given free access to laboratory chow and a ten percent sucrose solution. Animals injected with saline derived ten percent of their kilocalories from the chow and 90 percent from the sucrose solution. Those rats injected with NPY derived 48 percent of their energy from chow and 52 percent from the sucrose solution. The DAMGO-injected rats derived only 15 percent of their kilocalories from chow and the remainder from the sucrose solution. Thus, while NPY and DAMGO both stimulated energy intake compared to saline controls, the effect on intake of a palatable dilute energy solution versus a bland laboratory chow was different. The results of this study reinforce the notion that NPY has a major effect on energy needs, whereas opioids influence the rewarding characteristics of foods. Giraudo, S.Q., Grace, M.K., Billington, C.J., Levine, A.S. Differential Effects of Neuropeptide Y and the Mu-Agonist DAMGO on 'Palatability' vs. 'Energy'. Brain Research, 834(1-2), pp. 160-163, 1999.

Tolerance to Morphine-Induced Antinociception is Decreased by Chronic Sucrose or Polycose Intake

Chronic intake of palatable fluids alters morphine-induced antinociception. Two experiments were conducted to evaluate how long-term access to palatable fluids alters the development of tolerance to morphine-induced antinociception. In the first experiment, adult male Long-Evans rats were given one of the following to drink for a three weeks period: either a 0.15 percent saccharin solution, a 32 percent sucrose solution, a 32 percent Polycose solution, or chow and water alone (control). Half of the animals in each dietary condition were pre-exposed to 7.5 mg/kg morphine while the other half received saline. After injection, all rats were given a tail flick (TF) test. To determine whether tolerance developed, a cumulative dose paradigm was employed 1 week after the initial morphine injection, and this was repeated at weekly intervals for 3 weeks. Antinociception was significantly lower in rats pre-exposed to morphine. Although all rats displayed decreased antinociception relative to the first morphine injection, rats that drank saccharin showed greater reductions in morphine-induced antinociception relative to rats that drank sucrose or Polycose. A second experiment was conducted to determine whether the initial pairing of the TF with morphine pre-exposure produced differences in the development of opioid tolerance. All conditions and procedures were identical to those used in the first experiment except that the initial morphine and saline injections were not followed by TF. As in the first experiment, rats that drank saccharin showed less antinociception than rats that drank sucrose or Polycose. The present results suggest that long-term intake of palatable nutritive solutions curbs tolerance to morphine-induced antinociception, whereas long-term intake of a nonnutritive, sweet saccharin solution does not. D'Anci, K.E. Tolerance to Morphine-Induced Antinociception is Decreased by Chronic Sucrose or Polycose Intake. Pharmacology. Biochem. Behav., 63(1), pp. 1-11, 1999.

Cannabinoid Receptor Selectivity

The cannabimimetic ligand WIN 55212-2 is an aminoalkylindole that has been variously reported to have a 10-20 fold higher affinity for the peripheral CB2 receptor than for the CNS CB1 receptor. A recent report by NIDA grantees Reggio and Song has provided new insight into the molecular basis for the differences in selectivity. It had previously been shown that lysine 192 in the third transmembrane helix of the CB1 receptor was necessary to maintain binding of the "classical" cannabinoid structure HU-210 and that of the endogenous ligand anandamide. However, mutating the lysine to alanine did not change the binding of WIN 55212-2. Further, the carbonyl oxygen in the latter is not necessary for binding, and the morpholino ring can be replaced by an alkyl group without loss of binding. The researchers have modeled the interaction of WIN 55212-2 in its predominant s-trans conformation, and obtained the minimum interaction between the ligand and the transmembrane helices 3-5 of the CB1 and CB2 receptors. For the CB1 receptor, they have found an interaction between the naphthyl ring of the ligand and phenylalanine 189 in helix three, as well as with tryptophan 279 of helix five. There is also an interaction between the aromatic indole ring of the ligand and phenylalanine 200 in helix three. For the CB2 receptor, in addition to these three interactions, there is a fourth interaction between the indole ring and phenylalanine 197 in helix five. By expressing mutated receptors (changing phenylalanine 192 to valine in CB2 and making the corresponding valine to phenylalanine in CB1), the authors have shown a decrease in affinity of the ligand toward CB2 by 14 fold, and a corresponding increase in affinity toward the mutated CB1. The single amino acid mutation did not affect the binding of HU-210, the ligand CP-55940, or that of anandamide for either receptor. Inhibition of cyclic AMP accumulation was used as a functional assay measurement. The single point mutation in CB2 produced an increase in the concentration needed to yield a 50 percent inhibition of cAMP accumulation, consistent with a corresponding decrease in the binding affinity. The

selectivity of WIN 55212-2 for CB2 over CB1 was attributed in part to the presence of phenylalanine in transmembrane helix five. Song, Z.H., Slowey, C.A., Hurst, D.P., and Reggio, P.H., Molecular Pharmacology, 56(4), pp. 834-840, 1999.

Opiates, Nitric Oxide, Lungs and Blood Vessels

Dr. George Stefano and his co-workers, at SUNY Stony Brook, demonstrated that the endothelia from the human blood vessels express both delta and mu opioid receptors and the exposure of these cells to opioid peptides antagonize the morphine-stimulated release of nitric oxide in a dose-dependent manner. These findings suggest that opioid peptides and opiate alkaloids regulate endothelial function in an antagonistic manner, thereby influencing the micro-vascular environment. Stefano, G.B., Salzet, M., Hughes, T.K,, Bilfinger, T.V. Delta(2) Opioid Receptor Subtype on Human Vascular Endothelium Uncouples Morphine Stimulated Nitric Oxide Release. International Journal of Cardiology, Supplement 1, 64, pp. S43-51, 1998.

In another study, Dr. Stefano and his international colleagues reported activation of the mu3 opiate receptor by opiate alkaloids in tumor cells coupled with a rapid and substantial release of nitric oxide. From these findings the research suggests that "endogenous opiates, through their release of nitric oxide, may play a role in cancer progression." Fimiani, C., Arcuri, E., et al. Mu3 Opiate Receptor Expression in Lung and Lung Carcinoma: Ligand Binding and Coupling to Nitric Oxide Release. Cancer Letters, 146, pp. 45-51, 1999.

Fruit Flies Offer Insight Into Genes Involved In Response To Cocaine

In response to exposure to volatilized freebase cocaine, fruit flies (Drosophila) perform a set of behaviors similar to those observed in vertebrate animals, including grooming, proboscis extension, and unusual circling. Flies can show sensitization, increased severity of response, after even a single exposure to cocaine. Sensitization has been linked to the addictive process in humans and may be associated with craving. NIDA grantee Dr. Jay Hirsh of the University of Virginia and colleagues have demonstrated a connection between the biological clock and cocaine sensitization in fruit flies. Flies missing several genes that play a critical role in the insects' internal biological clock did not become sensitized to cocaine. Besides enabling the potential development of drugs to treat cocaine addiction, this research holds out the prospect that the "clock" genes, which are involved in setting and maintaining the body's internal clock, play other roles in the body and brain, such as affecting vulnerability to addiction. This research emphasizes the usefulness of flies as a model to unravel the complex genetics of drug abuse behavior. Andretic, R., Chaney, S., and Hirsh, J. Requirement of Circadian Genes for Cocaine Sensitization in Drosophila. Science, 285(5430), pp. 1066-1068, 1999.

EPH Molecules Mediate the Development of Reward Circuits

Dr. Renping Zhou and his colleagues at Rutgers University have found that interactions between the receptor EphB1 and the ligand ephrin B2 contribute to the establishment of distinct mesolimbic (VTA to nucleus accumbens) and mesostriatal (substantia nigra to caudate-putamen) pathways. They showed that this receptor ligand pair plays an important role in assuring that dopamine neurons from the ventral tegmental area connect with neurons in the nucleus accumbens and that dopamine neurons from the substantia nigra connect with neurons in the caudate-putamen or dorsal striatum. These molecules belong to the same family of tyrosine kinases (enzymes that phosphorylate a tyrosine amino acid in proteins) that control the development of the visual system and hippocampus. The ephrin B2 ligand is anchored to the membrane that enables it to guide the formation of nerve pathways. Receptor and ligand appear together in different brain regions. When paired, their interaction appears to inhibit neurite outgrowth and to even induce cell loss, perhaps preventing substantia nigra neurons from connecting with nucleus accumbens and prefrontal cortex neurons. Injections of cocaine and amphetamine induce the formation of this receptor-ligand pair in adult mice, suggesting the pair may play a role in the plasticity of adult dopamine nerve cells. This work is important because understanding how nerve pathways form aids in understanding their function and their relationships to each other. Revealing the molecular markers for developmental plasticity may lead to new insights into both the mechanisms of adult learning and the mechanisms of drug induced neuronal adaptation. Environmental influences during development may alter the neural circuitry of the brain and lead to increased susceptibility to drug addiction. Yue, Y., Widmer, D.A., Halladay, A.K., Cerretti, D.P., Wagner, G.C., Dreyer, J.L., Zhou, R. Specification of Distinct Dopaminergic Neural Pathways: Roles of the Eph Family Receptor EphB1 and Ligand Ephrin-B2. J. Neurosci., 19(6), pp. 2090-2101, 1999.

Serine Racemase: A Glial Enzyme Synthezing D-serine Regulates Glutamate-N-methyl-d-aspartate (NMDA) Neurotransmission

Ischemic brain injury or stroke can be a consequence of addiction to nicotine and cocaine. Much of the injury

resulting from ischemia in the brain is thought to be mediated by the activation of N-methyl-d-aspartate (NMDA) receptors through the massive release of glutamate. Activation of the NMDA receptor requires glutamate and coactivation at a "glycine" binding site on the NMDA receptor. D-serine is up to three times more potent than glycine as a coactivator of the NMDA receptor, and is released by glutamate from astrocytic processes that ensheath the synapse. Extracellular levels of endogenous D-serine are twice as high as glycine in the striatum, and D-serine is present at concentrations equal to glycine in the prefrontal cortex. This evidence suggests that D-serine acts as a neuromodulator on neurotransmitter in the brain. The discovery of D-serine as a modulator of synaptic transmission is surprising since D amino acids are prominent in bacteria but not in mammals. Until now the presence of D-amino acids in mammals has been attributed to dietary origin or intestinal bacteria. To show a physiological role for D-serine and that the enzyme is produced endogenously, the enzyme converting L-serine to D-serine must be identified. In the November 9, 1999 issue of PNAS Dr. Solomon Snyder and his group report the cloning of a serine racemase that converts L-serine to D-serine. The enzyme was cloned from rat brain using the partial amino acid sequence from a purified preparation of enzyme that converts L-serine to D-serine. The serine racemace enzyme was localized to astrocytes where D-serine is produced, which is consistent with the idea that cloned racemase is the major enzyme required for D-serine production. The cloning of this enzyme will permit scientists to generate large quantities of purified enzyme needed to develop drugs that block and activate serine racimase as well as characterize the role of serine racemace in NMDA neurotransmission. The development of selective inhibitors may provide treatment for stroke and neurodegenerative diseases that are mediated by glutamate excitotoxicity. Wolosker, H., Blackshaw, S., Snyder, S.H, Serine Racemase: A Glial Enzyme Synthesizing D-Serine to Regulate Glutamate-N-Methyl-D-Aspartate Neurotransmission. Proc. Natl. Acad. Sci., 96(23), pp. 13409-13414, 1999.

Knockout of the Nicotinic Receptor Subunit Alpha3: Possible Mouse Model for Rare Human Genetic Disease

The nicotinic acetylcholine receptor (nAchR) gene family consists of eight alpha subunits (a2-a9) and three beta subunits (Beta1-Beta3). These subunits can combine with one another in many different combinations to form diverse classes of nicotinic receptors in different regions of the nervous system and within the same nerve cell type. The alpha3 receptor subunit is expressed in autonomic ganglion that controls functions such as heart rate, urination, pupil size, and is expressed in brain regions such as pontine-mescencephalic micturation center. To test the physiological role that the alpha3 receptor plays, scientists at Columbia University led by Dr. Lorna Role and scientists at Baylor College of Medicine led by Dr. James Patrick and Dr. Arthur Beaudet generated a transgenic mouse lacking the alpha3 receptor subunit. Mice lacking the alpha3 receptor subunit have a growth deficiency, urinary retention, bladder stones, develop urinary tract infections, and widely dilated pupils. Drs. Role, Patrick and Beaudet suggest that urinary tract infections and urinary retention are caused by the absence of alpha3 containing nAchR in the parasympathetic intramural ganglia and may be caused by the lack of expression in the pontine-mescepahlic micturation. Drs. Role, Patrick and Beaudet also suggest that the failure of the pupils to constrict in response to bright light is caused by the loss of the alpha3 subunit in the superior cervical ganglion that mediates pupilary contraction to light. The phenotype of the mice lacking the alpha3 receptor subunit is similar to the rare human genetic disease known as megacystis-microcolon-intestinal hypoperstalsis syndrome (MMIHS) that is an autosomal recessive condition. Xu, W., Gelber, S., Orr-Urtreger, A., Armstrong, D., Lewis, R.A., Ou, C.N., Patrick, J., Role, L., De Biasi, M., Beaudet, A.L. Megacystis, Mydriasis, and Ion Channel Defect in Mice Lacking the alpha3 Neuronal Nicotinic Acetylcholine Receptor. Proc. Natl. Acad. Sci., 96(10), pp. 5746-51, 1999.

Retention of Supraspinal Delta-like Analgesia and Loss of Morphine Tolerance in Delta Opioid Receptor (DOR-1) Knock-out Mice

The delta opioid receptor (DOR-1) has been proposed to mediate several physiological functions including analgesia, tolerance, and reproduction. Pharmacological studies have suggested at least two DOR-1 subtypes. The delta 1(d1) receptor subtype is preferentially activated by the agonist [D-Pen2, D-Pen5] enkephalin (DPDPE) and antagonized by [D-Ala2, Leu5, Cys6] enkephalin (DALCE), while the delta 2(d2) receptor is preferentially activated by [D-Ala2, D-Glu4] deltorphin (deltorphin-2) and antagonized by naltrindole-5'-isothiocyanate (5'-NTII). This classification is further supported by analgesic, adenylyl cyclase and antisense approaches. NIDA grantee John E. Pintar of Robert Wood Johnson Medical School and his coworkers have recently discovered that disruption of the mouse delta opioid receptor by targeting exon 2 of the DOR-1 gene eliminates essentially all 3H-DPDPE and 3H-[D-Ala2, D-Glu4] deltorphin binding in the homozygous DOR-1 mutant mice, demonstrating that this locus encodes both the pharmacologically-defined d1 and d2 receptors. Disruption of the DOR-1 gene markedly reduced spinal delta analgesia, shifting the dose-response curve of DPDPE significantly to the right. Supraspinally, peptide delta agonists retained analgesic potency in thermal nociceptive assays that was only partially antagonized by naltrindole. Retained DPDPE analgesia was also demonstrated in the formalin test, while the nonpeptide delta agonist BW373U69 exhibited markedly enhanced activity in DOR-1 mutant mice as compared to wild-type mice. Together, these findings suggest

the presence of a second delta analgesic system mediated through a different opioid receptor. Finally, DOR-1 knockout mice do not develop analgesic tolerance to morphine, genetically demonstrating a central role for the DOR-1 receptor in this process. Zhu, Y., King, M.A., Schuller, A.G.P., Nitsche, J.F., Reid, M., Elde, R.P., Unterwald, E., Pasternak, G.W. and Pintar, J.E. Neuron, 24, pp. 243-252, 1999.

Role of Medial Prefrontal Cortex in Behavioral Sensitization

Behavioral sensitization to psychomotor stimulants in animal models can reveal neuroadaptations that are associated with the development of addiction to these drugs. Two such neuroadaptations in the mesoaccumbens dopamine (DA) system are DA autoreceptor subsensitivity in the ventral tegmental area (VTA) and DA D1 supersensitivity in the nucleus accumbens (NAc). Both behavioral sensitization to cocaine and these cellular correlates in the VTA and NAc were prevented by blockers of either the NMDA or the AMPA type of glutamate receptors. Similarly, lesions of the medial prefrontal cortex prevented behavioral and cellular manifestations of sensitization. These results indicate that excitatory, glutamatergic feedback connections from the medial prefrontal cortex are not only necessary for the induction of behavioral sensitization, but also are either directly or indirectly responsible for the neuroadaptations within the VTA and NAc that accompany the behavioral change. These results add to a growing body of evidence that implicates the medial prefrontal cortex in both the causes and consequences of drug addiction. Li, Y., Hu, X.T., Berney, T.G., Vartanian, A.J., Stine, C.D., Wolf, M.E., and White, F.J. Both Glutamate Receptor Antagonists and Prefrontal Cortex Lesions Prevent Induction of Cocaine Sensitization and Associated Neuroadaptations. Synapse, 34, pp. 169-180, 1999.

[Office of the Director][Report Index][Next Report Section]

Archive Home | Accessibility | Privacy | FOIA (NIH) | Current NIDA Home Page

National Institute on Drug Abuse

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

February, 2000

Research Findings

Behavioral Research

Some Abused Steroids Do Not Elicit Aggression in Rats

Marilyn McGinnis and her colleagues are examining the interaction between anabolic steroids and aggressive behaviors in rats under three conditions: different social contexts, different environmental contexts (home cage, opponent's cage, neutral territory), and under physical provocation (tail-pinch). Animals were treated with one of three steroids (testosterone propionate (TP), nandrolone decanoate (ND), or stanozolol (ST)) or with oil. In general, she found that TP produced the most aggression and animals treated with TP were less discriminating in their response to the provoking stimulus (any provocation would make them aggressive). ND and ST treatment was by far less effective in provoking aggression in the rats; often their levels of aggressive behavior were less than that seen in the controls. The magnitude of the androgenic effects of the three steroids on peripheral tissues paralleled their effects on aggressive behaviors. Testes weights were decreased only in the ST rats whereas ST and ND decreased the weights of the prostates and seminal vesicles. In contrast, TP increased the weights of these tissues. Thus ND and ST are not only less androgenic than TP, but may be anti-androgenic when compared to testosterone. Breuer, M., McGinnis, M., Possidente, B., Lumia, A.R. The Effects of Environmental, Social and Physical Manipulations on Male Rats Receiving Chronic Doses of Anabolic Androgenic Steroids. Soc. Behav. Neuroendocrinol., 3, p. 56, 1999.

A New Method for Measuring Heroin Addiction

Researchers at the University of Vermont used a self-report questionnaire to ask heroin- dependent patients about their preference for cigarettes and heroin at various hypothetical prices. The results from the simulation, in which no drugs were actually given to the patients, indicated that at low prices, cigarettes were preferred to heroin, but as price increased demand for heroin stayed relatively high while the demand for cigarettes declined. This simulation generated orderly measures of demand suggesting that this method can provide valuable information for assessing drug consumption habits. In addition, this method could be practically and easily used in a clinical setting as an adjunct method for assessing the severity of a patient's drug habit. Jacobs, E.A, and Bickel, W.K., Modeling Drug Consumption in the Clinic Via Simulation Procedures: Demand for Heroin Cigarettes in Opioid Dependent Outpatients. Experimental & Clinical Psychopharmacology 7, pp. 412-426, 1999.

Impulsivity and Cigarette Smoking

One characteristic of drug addiction is that drug-dependent individuals often choose to use an immediately available drug and forego prosocial delayed activities. This aspect of drug addiction is characterized as impulsive behavior. Investigators at the University of Vermont examined impulsive behavior in cigarette smokers, ex-smokers and persons who had never smoked. A delay discounting procedure was used in which no money was actually given to participants in the experimental setting, individuals were asked about their preferences for varying amounts of money that were either immediately available or could be received following a delay of several days to several months. For all individuals, the longer one had to wait for a given amount of money, the less that money was valued relative to a more immediately available amount. Interestingly, the researchers found that smokers, discounted money

significantly more than did either ex-smokers or persons who had never smoked. That is, delayed money was significantly less valuable for smokers than for the other groups studied. These data suggest that drug dependence is associated with greater impulsivity. These data further suggest that cigarette smoking, as with other forms of drug addiction, is associated with a rapid loss of subjective value for future outcomes. That impulsivity is associated with cigarette smoking suggests that impulsivity may relate to the drug effect and drug dependence directly given that cigarette smokers do not often suffer other life-disrupting consequences (e.g. homelessness, unemployment) associated with addiction to other drugs of abuse. Bickel, W.K., Odum, A.L., and Madden G.J. Impulsivity and Cigarette Smoking: Delayed Discounting in Current, Never, and Ex-smokers. Psychopharmacology, 146, pp. 447-454, 1999.

Effects of Dopamine Receptor Antagonists on Cocaine Smoking

In determining the effectiveness of a pharmacological therapy for drug addiction, it is not only important to consider the therapy's neuropharmacological properties in relation to the drug of abuse, but also to consider the environmental factors that may contribute to the effectiveness of the therapy. Using an animal model of crack cocaine abuse, researchers recently reported that the "price" of crack can determine how effective dopamine antagonists are in reducing crack cocaine smoking. Dopamine is one of the major neurotransmitters that mediates cocaine's action and its rewarding properties in the brain. The researchers tested two compounds that block dopamine's action at specific dopamine brain receptors. One drug is designed to specifically block cocaine at the dopamine D1 receptor (SCH 23390) and the other drug is designed to block its effects at the D2 (raclopride) receptor. The investigators found that following the administration of either antagonist, crack cocaine consumption remained high at most prices for cocaine, except at the highest prices. That the antagonists were only effective when crack was available at a relatively "high price," suggests that these dopamine antagonists, at the doses tested, have limited efficacy in treating cocaine abuse. Campbell, U.C., Rodefer, J.S., and Carroll, M.E. Effects of Dopamine Receptor Antagonists (D1 and D2) on the Demand for Smoked Cocaine Base in Rhesus Monkeys. Psychopharmacology 144, pp. 381-388, 1999.

Neuroactive Steroids are Self-Administered by Monkeys

Pregnane steroids are present in the nervous system. These neuroactive steroids, instead of binding at a genomic (steroid) receptor, have high affinity for a recognition site on the GABA-A receptor complex. Endogenous neuroactive steroids are elevated in the brain during stressful life events and at the time of menstruation in females. NIDA grantee Dr. James Rowlett (presently at Harvard Medical School) and colleagues tested the pregnane steroid, pregnanolone, for self-administration in monkeys. Their finding that all animals tested did self-administer pregnanolone suggests that progesterone-derived compounds may have central reinforcing properties. This and other studies using animal models suggests that stress can lead to drug self-administration, and may cause drug relapse following abstinence. However, the neural events underlying stress induced relapse have not yet been identified. Dr. Rowlett's findings suggest that activation of endogenous steroid systems in the brain may be a substrate for stress induced influences on drug seeking behavior, possibly by enhancing or mimicking central reinforcement. Rowlett, J.K., Winger G., Carter, R.B., Wood, P.L., Woods, J.H., and Woolverton, W.L. Reinforcing and Discriminative Stimulus Effects of the Neuroactive Steroids Pregnanolone and Co 8-7071 in Rhesus Monkeys. Psychopharmacology, 145, pp. 205-212, 1999.

A Role for Serotonin in the Neurobiological Substrate for Incentive Motivation

Environmental stimuli previously associated with drugs of abuse take on motivational properties of their own and may prompt cravings or direct continued drug seeking behaviors. The neurobiological circuitry underlying the formation of these learned associations has yet to be identified. Using animal drug self-administration paradigms, researchers have found the brain neurotransmitter serotonin (5-HT) is involved in the development of the direct reinforcing effects of drugs such as cocaine. Some reports also suggest that 5-HT activation is important in self-reported craving for drug in human cocaine abusers. Recent reports from the laboratory of Dr. Janet Neisewander at Arizona State University suggest that these central 5-HT systems serve as a critical component in drug-seeking behavior. To test this hypotheses, Dr. Neiswander trained animals to self-administer cocaine and after cocaine availability ceased, she assessed them for 'relapse' in the presence of drug-associated cues (incentive motivational stimuli). She found that animals with low levels of 5-HT in the central nervous system exhibited significantly less cocaine 'seeking' behavior during extinction from drug self-administration. By contrast, animals with reduced 5-HT levels who had been trained to respond for food rewards, and then extinguished showed normal cue-induced food seeking. Tran-Nguyen, L.T.L., Baker, D.A., Grote, K.A., Solano, J., and Neisewander, J.L. Serotonin Depletion Attenuates Cocaine-Seeking Behavior in Rats. Psychopharmacology, 146, pp. 60-66, 1999.

The Role of Endogenous Stress Systems in Priming a Relapse to Drug-Seeking Behavior

In the September 1999 Director's Report to Council some interesting new findings from the laboratory of Dr. Nick Goeders at Louisiana State University Medical Center were reported, suggesting that although pain stimuli and cocaine may have similar internal 'cue' properties, this shared discriminative effect could not account for the ability of painful stimuli to prompt cocaine-seeking behavior in animal self-administration procedures. Now Dr. Goeders has investigated the role of brain adrenocorticosteroids in the priming effect. Priming is demonstrated when previously drug-experienced animals, after receiving a single dose of a drug, are observed to relapse to previous patterns of drug seeking behavior (e.g., again make 'trained' responses to receive the drug). When the animals received a drug that blocks adrenocorticosteroid synthesis - thus blunting internal stress systems - the priming effect of cocaine was not seen. These data suggest that although cocaine-induced priming has been observed to raise plasma corticosterone, priming does not seem critically dependent upon activation in these brain stress systems. Mantsch, J.R., and Goeders, N.E. Ketoconazole Does Not Block Cocaine Discrimination or the Cocaine-Induced Reinstatement of Cocaine-Seeking Behavior. Pharmacology, Biochemistry and Behavior, 64, pp. 65-73, 1999.

Central Dopamine D3 Receptor Substrates in Cocaine-Induced Conditioned Place Preference

Dr. Janet Neisewander from the University of Arizona has been studying a potential role for central dopamine D3 receptor substrates in the reinforcing properties of cocaine. She has employed conditioned place preference (CPP) techniques to examine an animal's preference for environments previously paired with the administration of cocaine. In her studies, the mixed D2/D3 agonist 7-OH-DPAT attenuated the development of cocaine-induced CPP. This observation is different from results reported from Dr. George Koob's laboratory in 1998, wherein 7-OH-DPAT was found to potentate the reinforcing properties of cocaine with self-administration procedures. Collectively, these results might indicate that D3 substrates play a different role in direct reinforcing properties of the drug than the role they play in the acquisition of incentive motivational properties by stimuli associated with drug rewards. Alternatively, this substrate may be differentially involved in the acquisition versus the maintenance of ongoing drug-seeking behaviors. Khroyan T.V., Fuchs, R.A., Beck, A.M., Groff, R.S., and Neisewander, J.L. Behavioral Interactions Produced by Co-administration of 7-OH-DPAT with Cocaine or Apomorphine in the Rat. Psychopharmacology, 142, pp. 383-392, 1999.

Conditioned Increase in Place Preference by Access to Novel Objects: Antagonism by MK-801

A series of studies examined if the conditioned place preference preparation would prove useful in studying the appetitive quality of novelty, assessed whether iv cocaine would also condition an increase in preference, and assessed the role of the N-methyl-D-aspartate (NMDA) receptor in this place conditioning paradigm. In 3 separate place conditioning experiments with 95 male rats, repeated access to novel objects in one of 2 distinct environments conditioned an increase in preference for the novelty-paired environment. A conditioned increase in preference was found whether novel objects were paired with a randomly chosen environment or with the less preferred of 2 environments (conditioned against a preference). This enhanced preference did not depend on the control group employed. Iv infusions of cocaine also produced an increase in preference using the procedures employed with novel objects. Pretreatment with the NMDA receptor antagonist MK-801 blocked acquisition of the enhanced place preference conditioned by access to novel objects without decreasing time spent with objects or inducing a place aversion in controls. Bevins, R.A., and Bardo, M.T. Conditioned Increase in Place Preference by Access to Novel Objects: Antagonism by MK-801. Behav. Brain Res, 99, pp. 53-60, 1999.

The Effects of Anxiolytic Drugs on Place Preference

This study assessed whether novelty-induced place preference resulted from an avoidance of the stress-related familiar compartment or approach to a novel compartment in rats. Seven to eight subjects per group were injected with 0.1, 0.3, 1.0, 3.0 mg/kg of diazepam in Experiment 1a, and 0 or 3.0 mg/kg of diazepam in Experiment 1b prior to a preference test. In Experiment 2, 8 subjects per group were injected with gepirone (0.1, 0.3, 1.0 mg/kg) prior to a preference test. Control subjects showed a novelty-induced place preference. Novelty-induced place preference was disrupted by diazepam, but only at a dose (3 mg/kg) that also decreased locomotor activity. Gepirone failed to alter the preference behavior, even at a dose (1 mg/kg) that decreased locomotor behavior. In Experiment 3, 14 rats, equally exposed to the compartments, were given a choice between the compartments, one had had a novel object placed in it. Subjects spent more time in a familiar compartment that contained the novel object than in a familiar compartment with no new object. Results indicate that preference for the novel compartment may reflect the rewarding effect of novelty rather than aversion to the familiar. Klebaur, J.E., and Bardo, M.T. The Effects of Anxiolytic Drugs on Novelty-Induced Place Preference. Behavioural Brain Research, 101, pp. 51-57, 1999.

Heroin Reward in Economic Terms

Recent theories of substance abuse have used value discounting of delayed rewards to partly explain the decision to take drugs. Normative-economic theory holds that an exponential function describes the effects of delay on discounting, whereas the matching law posits a hyperbolic discounting function. The ability of these functions to describe 18 human heroin-dependent individuals' monetary- and heroin-reward delay-discounting functions was assessed. In the 1st condition, participants chose to bet monetary rewards. Delayed rewards were $1,000, and the immediate reward amount was adjusted until choices reflected indifference. In the 2nd condition, participants chose between immediate and delayed heroin (the delayed amount was that which each participant reported he or she could purchase with $1,000). The hyperbolic function produced significantly higher R2 values and significantly lower sums of squared error values. Consistent with previous findings, delayed heroin rewards were discounted at a significantly higher rate than were delayed monetary rewards. Madden, G.J., Bickel, W.K., and Jacobs, E.A. Discounting of Delayed Rewards in Opioid-Dependent Outpatients: Exponential or Hyperbolic Discounting Functions? Exp Clin Psychopharm, 7(3), pp. 284-293, 1999.

[Office of the Director][Report Index][Next Report Section]

Archive Home | Accessibility | Privacy | FOIA (NIH) | Current NIDA Home Page

National Institute on Drug Abuse

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

February, 2000

Research Findings

Treatment Research and Development

Buprenorphine Dosing Every 3 or 4 Days

Dr. Warren Bickel and associates at the University of Vermont recently conducted a study comparing 24-, 48-, 72-, and 96-hour buprenorphine dosing regimens in opioid-dependent outpatients. Fourteen subjects received buprenorphine in a double-blind, placebo-controlled crossover trial. Daily sublingual maintenance doses were 4 mg/70 kg (n = 5) and 8 mg/70 kg (n = 9). After a stabilization period of maintenance administration, subjects received, in a random order, four dosing regimens for five repetitions of each regimen: a maintenance dose every 24 hours, a doubled maintenance dose every 48 hours, a tripled maintenance dose every 72 hours, and a quadrupled maintenance dose every 96 hours. In the latter three dosing regimens, subjects received placebo on the interposed day(s). Study participation was contingent on opioid abstinence and daily clinic attendance. Measures of subjective opioid agonist and withdrawal effects were assessed daily. Results indicated that relative to standard maintenance dosing, none of the higher doses induced agonist effects. Changes in indices of subjective withdrawal effects were noted as the time since the last active dose increased during intermittent dosing regimens, but the magnitude of these effects was relatively low and was comparable to those found in other alternate-day dosing studies. These results support the feasibility and safety of twice weekly buprenorphine dosing regimens. Petry, N.M., Bickel, W.K. and Badger, G.J. A Comparison of Four Buprenorphine Dosing Regimens in the Treatment of Opioid Dependence. Clin Pharmacol Ther, 66(3), pp. 306-314, 1999.

LAAM is Not Less Potent than Methadone

Levo-alpha-acetylmethadol (LAAM) and methadone are full mu-opioid agonists used to treat opioid dependence. Current labeling indicates that LAAM is less potent than methadone. Clinical studies have not determined the relative potency of these drugs. This study conducted at Johns Hopkins University compared the effects of acute doses of LAAM and methadone and also examined the ability of naloxone to reverse their effects. Five occasional opioid users received once weekly doses of either placebo, LAAM, or methadone (15, 30, or 60 mg/70 kg p.o.) in agonist exposure sessions and then received naloxone (1.0 mg/70 kg i.m.) 24, 72, and 144 h after agonist exposure. Subject-rated, observer-rated, and physiological measures were assessed regularly. Comparisons of physiological and subjective measures collected in agonist exposure sessions indicate that LAAM is not less potent than methadone under acute dosing conditions. For some measures, LAAM was significantly more potent. Three subjects who entered the study were withdrawn for safety reasons due to greater than anticipated and clinically relevant respiratory depression after receiving 60 mg of LAAM. Naloxone did not fully reverse the pupil constriction produced by 60 mg of LAAM. Acute agonist effects suggest that LAAM may be more potent than methadone and more potent than current labeling indicates. An accurate LAAM:methadone relative potency estimate will aid determination of adequate doses for opioid-dependent patients inducted onto LAAM and for methadone maintenance patients who choose to switch to more convenient thrice-weekly LAAM. Relative Potency of Levo-alpha-acetylmethadol and Methadone in Humans Under Acute Dosing Conditions. Eissenberg, T., Stitzer, M.L., Bigelow, G.E., Buchhalter, A.R., and Walsh, S.L. J Pharmacol Exp Ther., 289(2), pp. 936-945, 1999.

Smoking, Schizophrenia, and Clozapine

Of patients with schizophrenia, 70 to 80% smoke. Nicotine corrects certain information processing and cognitive psychomotor deficits seen in many patients with schizophrenia. Clozapine, but not conventional antipsychotics, has been shown to correct some of these deficits. Investigators from Duke University assessed psychopathology and smoking in 70 patients with treatment refractory schizophrenia (55 smokers and 15 nonsmokers) at baseline when they were receiving conventional antipsychotics and again after they were switched to clozapine. Smokers showed significantly greater therapeutic response to clozapine than nonsmokers. Smokers smoked less when treated with clozapine than when treated with conventional antipsychotics. The authors concluded that certain patients with schizophrenia have contributing pathophysiologic mechanisms that respond favorably to either nicotine or clozapine. McEvoy, J.P., Freudenreich, O., and Wilson, W.H. Smoking and Therapeutic Response to Clozapine in Patients with Schizophrenia. Biol Psychiatry, 1;46(1), pp. 125-9, 1999.

Nicotine Withdrawal and PMS

Investigators at the University of Minnesota used an inpatient setting to test the hypothesis that withdrawal symptoms in short-term smoking cessation in women were increased in the late luteal phase when pre-menstrual symptomatology is the highest. Twenty-one female smokers with clinical, anatomical, and hormonal verification of their menstrual cycle phase were randomized to either a smoking abstinence group (n = 16) or a continued smoking group (n = 5). Participants were admitted during alternate phases of their cycle for two 7-day admissions with a 1-month interim period when they resumed smoking. Nicotine withdrawal scores, Smoking Urges scores and Pre-menstrual Assessment scores were collected during 2 days of baseline and 5 days of smoking deprivation. Smoking behavior was documented by self-report, breath CO levels and saliva cotinine measurements. Withdrawal symptomatology was not affected by menstrual cycle phase during short-term cessation in spite of increased pre-menstrual changes seen in the late luteal phase. In addition, no phase effect on smoking behavior was detected and cigarette consumption remained stable across the cycle in both groups. These results suggest that for some smoking cessation studies, complex strategies to control for menstrual cycle effects may not be necessary. However, Smoking Urges scores did suggest increased desire to smoke and desire to relieve negative affect in the late luteal phase when women have higher pre-menstrual symptomatology. This suggests women may have greater difficulty quitting smoking in late luteal phase, and it seems prudent to recommend that women quit during the follicular phase of their cycle. Allen, S.S., Hatsukami, D.K., Christianson, D., and Nelson, D. Withdrawal and Pre-Menstrual Symptomatology During the Menstrual Cycle in Short-Term Smoking Abstinence: Effects of Menstrual Cycle on Smoking Abstinence. Nicotine & Tobacco Research, 1, pp. 129-142, 1999.

Bupropion Helps Patch Prevent Smoking Relapse

Researchers from the University of Wisconsin conducted a double-blind, placebo-controlled comparison of sustained-release bupropion (244 subjects), a nicotine patch (244 subjects), bupropion and a nicotine patch (245 subjects), and placebo (160 subjects) for smoking cessation. Smokers with clinical depression were excluded. Treatment consisted of nine weeks of bupropion (150 mg a day for the first three days, and then 150 mg twice daily) or placebo, as well as eight weeks of nicotine-patch therapy (21 mg per day during weeks 2 through 7, 14 mg per day during week 8, and 7 mg per day during week 9) or placebo. The target day for quitting smoking was usually day 8. The abstinence rates at 12 months were 15.6 percent in the placebo group, as compared with 16.4 percent in the nicotine-patch group, 30.3 percent in the bupropion group ($P<0.001$), and 35.5 percent in the group given bupropion and the nicotine patch ($P<0.001$). A total of 311 subjects (34.8 percent) discontinued one or both medications. Seventy-nine subjects stopped treatment because of adverse events: 6 in the placebo group (3.8 percent), 16 in the nicotine-patch group (6.6 percent), 29 in the bupropion group (11.9 percent), and 28 in the combined-treatment group (11.4 percent). The most common adverse events were insomnia and headache. Treatment with sustained-release bupropion alone or in combination with a nicotine patch resulted in significantly higher long-term rates of smoking cessation than use of either the nicotine patch alone or placebo. Abstinence rates were higher with combination therapy than with bupropion alone, but the difference was not statistically significant. Jorenby, D.E., Leischow, S.J., Nides, M.A., Rennard, S.I., et al. A Controlled Trial of Sustained-Release Bupropion, A Nicotine Patch, or both for Smoking Cessation. N Engl J Med, 340(9), pp. 685-691, 1999.

Smokeless Tobacco Cessation

Smokeless tobacco use is increasing in the United States, especially among young men, but there are few resources to assist users in quitting their use of moist snuff or chewing tobacco. This article reviewed some unique aspects of smokeless tobacco use and provided a systematic four-step clinical plan for providing a cessation program. The authors provided clear suggestions, measures, and aids for getting the user ready to quit, planning their quit, quitting, and staying quit. The procedures and measures were validated in randomized clinical trials and provide

empirical support for the recommended cessation procedures. Finally, a review of brief cessation interventions in the context of health care was provided. Severson, H.H., and Hatsukami, D. Prim Care, 26(3), pp. 529-551, 1999.

Brain Metabolite Changes in Opiate Abusers in Methadone Maintenance

Dr. Marc Kaufman and colleagues at the Brain Imaging Center at McLean Hospital evaluated cerebral phosphorus metabolites using phosphorous magnetic resonance spectroscopy (P-MRS) in opiate-dependent polydrug abusers (6 men, 9 women; 40+5 years old) in methadone maintenance therapy (MMT) to determine if metabolite profiles differed based on treatment duration. Study subjects included two groups: one on MMT for an average of 39 weeks (n=7) and another on MMT for an average of 137 weeks (n=8). These groups were age-and body mass index (BMI)-matched. Results revealed that MMT subjects differed from controls in percent phosphocreatine (%PCr) levels and in both phosphomonoester (%PME) and phosphodiester (%PDE), which are thought to reflect abnormalities in energy and phospholipid metabolism, respectively. In short-term MMT subjects, abnormal %PCr (-18), % PME (+20), and %PDE (+17) levels were found compared to controls. However, in long-term MMT subjects, the only metabolite abnormality detected was in %PCr (-9) despite continued illicit drug abuse. From these data, the authors concluded that polydrug abusers in MMT have results consistent with abnormal brain metabolism and phospholipid balance. Interestingly, the nearly normal metabolite profile in long-term MMT subjects suggests that prolonged MMT might be associated with improved neurochemistry. Kaufman, M.J., Pollack, M.H., Villafurte, R.A., Kukes, T.J., Rose, S.L., Mendelson, J.H., Cohen, B.M., and Renshaw, P.F. Cerebral Phosphorous Metabolite Abnormalities in Opiate-Dependent Polydrug Abusers in Methadone Maintenance. Psychiatry Research: Neuroimaging, 90, pp. 143-152, 1999.

Cerebral Alterations in Recreational MDMA Users

Dr. Linda Chang and colleagues at the UCLA School of Medicine evaluated the effects of recreational use of MDMA on brain neurochemistry. Twenty-two MDMA users were evaluated with magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (MRS) in the mid-frontal, mid-occipital, and parietal brain regions, and results were compared to matched controls. MRS showed normal N-acetyl (NA) compounds in all brain regions. The myo-inositol (MI) concentration and the MI to creatine (CR) ratio were increased in the parietal white matter in MDMA users. Cumulative lifetime dose of MDMA showed significant effects on MI concentration in the parietal white matter and occipital cortex. Normal NA concentration levels suggested a lack of significant neuronal injury in recreational MDMA users. However, the usage-related increase in MI suggests that exposure to MDMA, even at recreational doses, might cause increased glial content. Chang, L. et al. Cerebral 1H MRS Alterations in Recreational 3,4-Methylenedioxy-methamphetamine (MDMA, "Ectasy") Users. J. Mag Res Imaging, 10, pp. 521-526, 1999.

Neurochemical Adaptation to Cocaine Abuse

Drs. Shi-Jiang Li, Eliott Stein and their colleagues at the Milwaukee College of Medicine used an advanced brain imaging technique, magnetic resonance spectroscopy (MRS), to demonstrate a potential neurotoxic effect of chronic cocaine use in humans. Twenty-one cocaine abusers and 12 age-matched controls had *in vivo* proton MRS scans. Proton spectra were obtained from single voxels in the left basal ganglia and left thalamus. The cocaine users exhibited a 17% lower level of N-acetyl aspartate in the left thalamus, but not left basal ganglia compared to the control subjects. Since N-acetyl aspartate levels are thought to be an index of neuronal integrity, these results suggest that chronic cocaine use is associated with neurochemical dysregulation and possibly neurotoxicity in the thalamus. Since subjects were only abstinent from cocaine for 24 hours prior to the scan it will be necessary to determine whether this neurochemical abnormality disappears with continued abstinence from cocaine. It is also possible that the observed differences between cocaine users and controls existed prior to the onset of drug use. It also remains to be determined what impact this neurochemical abnormality has on behavioral or cognitive functioning, especially given the critical role of the thalamus in regulating input to the cerebral cortex. Li, S.-J. et al., Neurochemical Adaptation to Cocaine Abuse: Reduction of N-acetyl Aspartate in Thalamus of Human Cocaine Abusers. Biological Psychiatry, 45, pp. 1481-1487, 1999.

Dynorphin A1-13 Elevation of Serum Prolactin Levels through Opioid Receptor Mechanism in Humans: Gender Differences and Implications for Modulation of Dopaminergic Tone in Addictions Treatment

Dr. Mary Jeanne Kreek and colleagues at the Rockefeller University conducted a study to determine whether dynorphin peptides act to lower dopaminergic tone in the tuberoinfundibular system, resulting in elevated serum prolactin levels and, if so, whether such an effect is mediated by the opioid receptors. Dose-related increases in serum prolactin levels were observed after administration of dynorphin A_{1-13} in healthy human volunteers with no history of drug or alcohol abuse. Studies were then conducted to determine if this effect is opioid receptor-mediated

and, if so, whether at the kappa or mu types. Pretreatment with the opioid antagonist, nalmefene, which has high affinity at both kappa- and mu-opioid receptors, caused a greater attenuation in dynorphin A_{1-13}-stimulated increases in serum prolactin levels than pretreatment with similarly high doses of naloxone, an antagonist with lower affinity for both kappa- and mu-opioid receptors. These results suggest dynorphin A_{1-13} lowers tuberoinfundibular dopaminergic tone through action at kappa- and possibly mu-opioid receptors. Female subjects were significantly more responsive to the prolactin effects of dynorphin than were male subjects. Dynorphin gene expression, dynorphin peptides, and kappa-opioid receptor gene expression and binding have been shown to be altered in response to cocaine administration. Additionally, both dynorphin peptides and kappa-opioid agonists have been shown to lower dopamine levels in the nucleus accumbens and to attenuate cocaine-induced surges in dopamine levels. The authors suggest that a dynorphin-like compound that is capable of affecting critical mesolimbic-mesocortical and nigrostriatal dopaminergic systems might be effective in the management of cocaine addiction. Kreek, M.J. et al., Dynorphin A_{1-13} causes elevation of serum levels of prolactin through an opioid receptor mechanism in humans: Gender Differences and Implications for Modulation of Dopaminergic Tone in the Treatment of Addictions. J. Pharmacol. Exp. Therap., 288, pp. 260-269, 1999.

Concurrent and Predictive Validity of Antisocial Personality Disorder Subtyping Among Substance Abusers

Three hundred and seventy inpatient and outpatient substance abusers were divided according to presence and subtype of antisocial personality disorder (APD) into groups comparing: a) adult antisocial behavior (AAB) versus full APD; b) APD with low versus high sociopathy; c) APD with versus without lifetime depression; and d) APD with versus without other axis II disorders. Multivariate regression was used to predict the unique contribution to the variance in baseline and 12-month follow-up measures of substance use, psychiatric severity, and personality. The presence of comorbid axis II pathology was the strongest predictor of baseline severity in all three domains. APD substance abusers with lifetime depression exhibited greater baseline to follow-up reductions in psychiatric severity than those APD substance abusers without a history of depression. All APD subtypes improved over time with treatment, suggesting that this diagnosis does not necessarily indicate poor prognosis. Cecero, J., Ball, S., Tennen, H., Kranzler, H., and Rounsaville, B. J. Nerv and Ment. Dis, 187, pp. 478-486, 1999.

Substance Dependence Posttraumatic Stress Disorder Therapy: An Integrated Cognitive-Behavioral Approach

While substance abuse and PTSD are known to frequently co-occur, there have been few clinical trials evaluating integrated approaches for this form of dual diagnosis. Substance Dependence PTSD Therapy (SDPT) is the first manualized individual treatment to undergo a controlled clinical trial. SDPT is a 5 month, twice-weekly, two-phase individual cognitive-behavioral treatment utilizing (a) relapse prevention and coping skills training for substance abuse; and (b) psychoeducation, stress inoculation training, and *in vivo* exposure for PTSD. SDPT is also unique in having been designed for use in mixed-gendered civilians with varied sources of trauma. Preliminary data from this study indicates efficacy in reducing PTSD severity. Triffleman, E., Carroll, K., and Kellogg, S. J. Substance Abuse Treatment, 17, pp. 3-14, 1999.

Day Treatment Versus Enhanced Standard Methadone Services for Opioid-Dependent Patients: a Comparison of Clinical Efficacy and Cost

Dr. Kelly Avants and colleagues at Yale University evaluated the differential efficacy and relative costs of two intensities of treatment (intensive day treatment versus enhanced standard care) for methadone maintained opioid-dependent patients. 291 patients participated in a 12-week randomized clinical trial with 6-month follow-up. The day treatment was an intensive, 25-hour per-week program. The enhanced standard care was standard methadone maintenance plus a weekly skills training group and referral to services. Both interventions were manual-guided. No significant differences were found between the two groups in use of either opiates or cocaine. Drug use, drug-related problems, and HIV risk behaviors decreased significantly for patients assigned to both treatment intensities. Thus, the intensive day treatment program, which cost significantly more, was not cost effective, relative to an enhanced methadone maintenance program, which produced comparable outcomes. Avants, S.K., Margolin, A., Sindelar, J.L., Rounsaville, B.J., Schottenfeld, R., Stine, S., Cooney, N.L. Rosenheck, R.A., Ki, S.H., and Kosten, T.R. American Journal of Psychiatry, 156, pp. 27-33, 1999.

Validity of Diagnostic Criteria for Adolescent Alcohol and Cannabis Use Disorders

Until recently, few studies focused on adolescent drug abuse utilized formal diagnostic criteria for substance use disorders. Reluctance to use diagnostic criteria was, in part, based on concerns that adult-based criteria and related

diagnostic instruments were not developmentally appropriate for adolescent patient populations. But utilization of a common set of criteria and related measures would facilitate cross-study comparisons and collaborations in drug treatment research. Toward identifying adolescent-appropriate criteria, Dr. Winters and colleagues at the University of Minnesota School of Medicine examined DSM-III-Revised and DSM-IV criteria for alcohol and cannabis use disorders in a sample of 772 adolescents (42% 12-15 years; 63% boys; 77% white) enrolled in outpatient drug treatment. Results indicate that, compared to DSM-III-Revised criteria, application of DSM-IV criteria for alcohol and cannabis use results in more abuse cases and fewer dependence cases, with the shift in diagnostic assignments largely due to a broadening of abuse criteria rather than a tightening of dependence criteria when applied to adolescents. Although further research is necessary, external validity supported the DSM-IV abuse and dependence distinction in this adolescent patient population. Winters, K.C., Latimer, W., and Stinchfield, R.D. J. Studies on Alcohol, 60, pp. 337-344, 1999.

Desipramine May Be A Useful Adjuctive Medication In Facilitating Opioid and Cocaine Abstinence In Opioid-Maintained Patients

The efficacy of opioid medications to treat opioid and cocaine dependence may differ by sex. A 13-week randomized, double-blind, placebo controlled trial evaluated the efficacy of desipramine hydrochloride (0 or 150 mg/d) plus buprenorphine (12 mg/d) or methadone (65 mg/day) in 180 opioid-dependent cocaine abusers (124 men and 56 women). Urine samples were obtained thrice weekly, and self-reported cocaine and heroin use was reported weekly. In men, opioid dependence was increased more rapidly over time when treated with methadone than with buprenorphine, whereas cocaine abstinence was increased more with buprenorphine than with methadone. In women, opioid abstinence was increased the least rapidly when treated with buprenorphine plus placebo, while cocaine abstinence was increased more rapidly over time when treated with methadone than with buprenorphine. Regardless of sex or opioid medication, desipramine increased opioid and cocaine abstinence over time more rapidly than placebo. Desipramine plasma levels were higher in women than men. Higher desipramine plasma levels were associated with greater opioid but not cocaine abstinence. Desipramine in Opioid-dependent Cocaine Abusers maintained on Buprenorphine vs. Methadone, Oliveto, A., Feingold, A., Schottenfeld, R., Jatlow, P., and Kosten, T. Arch Gen Psychiatry, 56, pp. 812-820, 1999.

[Office of the Director][Report Index][Next Report Section]

Archive Home | Accessibility | Privacy | FOIA (NIH) | Current NIDA Home Page

National Institute on Drug Abuse

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

February, 2000

Research Findings

Research on AIDS and Other Medical Consequences of Drug Abuse

Behavioral Practices and Therapies for HIV/AIDS

A study assessed knowledge and utilization of, and adherence to, combination antiretroviral therapies including protease inhibitors among 210 low-income 18-52 year olds living with HIV/AIDS. Most (65%) had received protease inhibitors at some point, although only 54% had received them in the previous 3 months. Parents with AIDS were more likely to have taken protease inhibitors than young adults (72% vs 33%). About half of those taking combination antiretroviral therapies reported consistent adherence (55%), even among the 64% who experienced side effects. However, the reliability of these reports appears moderate. More than half of those taking combination therapies reported improvements in their health (62%) Eighty seven percent of subjects reported having their viral loads tested on average 3.7 times. More than one third reported undetectable viral loads. Subjects were moderately informed about protease inhibitors. Those who abstained from substance use were more likely to be adherent, and adherence was not related to sexual behavior. These reports suggest that persons with AIDS are at risk for developing treatment-resistant strains of HIV because half or fewer have adequate levels of adherence, and further, a substantial minority are not on approved combination therapies. Gwadz, M., De Vogli, R., Rotheram-Borus, M.J., Diaz, M.M., Cisek, T.J., Nionne B., and Tottenham, N. Behavioral Practices Regarding Combination Therapies for HIV/AIDS. Journal of Sex Education & Therapy, 24, pp. 81-88, 1999.

Coping Ability among HIV + and - Female Injection Drug Users

This study examined the psychosocial determinants of coping ability in a cohort of 249 HIV positive and HIV negative female injection drug users (IDUs), using a cross-sectional retrospective design. Information collected using a structured questionnaire included data on psychosocial risk and protective factors in the personality, family, and peer domains, HIV status, and coping ability. Coping ability was associated with conventionality, greater control of emotions, less psychopathology, and family cohesion in both HIV positive and HIV negative subjects. The psychosocial factors affected coping in HIV positive and HIV negative IDUs via two different mediational models. The interactional findings supported the influence of risk/protective interactions in both groups. The findings demonstrate the impact of the interplay between personality factors and external support on coping ability in female IDUs. Brook, D.W., Brook, J.S., Whiteman, M., Roberto, J., Masci, J.R., Amundsen, F., and de Catalogne, J. Coping Among HIV Negative and HIV Positive Female Injection Drug Users. AIDS Educ Prev, 11(3), pp. 262-273, 1999.

Coping Strategies of HIV + and HIV - Female Injection Drug Users

This study examined longitudinally the psychosocial correlates of coping strategies among 165 HIV positive and 179 HIV negative female injection drug users (IDUs). Participants were interviewed twice using a structured questionnaire, with a 6-month interval between interviews. The questionnaire included psychosocial measures as well as measures of general coping and specific HIV-related coping. Data were analyzed using logistic regression analyses. The findings indicated that favorable factors in the psychosocial domains at Time 1 were significantly associated with an increased likelihood at Time 2 of the use of general coping and specific adaptive coping strategies, such as

problem solving and seeking social support, and with a decreased likelihood at Time 2 of the use of maladaptive coping strategies, such as aggression and the use of illicit drugs. These findings highlight particular areas of psychosocial functioning that can be targeted by intervention programs to promote adaptive coping and minimize maladaptive coping among HIV positive and HIV negative female IDUs. Brook, D.W., Brook, J.S., Richter, L., Whiteman, M., Win, P.T., Masci, J.R., and Roberto, J. Coping Strategies of HIV-Positive and HIV-Negative Female Injection Drug Users: A Longitudinal Study. AIDS Educ Prev, 11(5), pp. 373-388, 1999.

Preventing Adolescent Health Risk Behaviors

The purpose of this study was to examine 6-year follow-up data on adolescent health-risk from a nonrandomized controlled trial of an intervention combining teacher training, parent education, and social competency training. Two intervention conditions were studied. The full program provided intervention components in grades 1 through 6, the later intervention program was provided in only grades 5 and 6; students in the current follow-up sample were 18 years of age. Results indicate that compared to control group students, the full intervention group students reported significantly fewer violent acts, less heavy drinking, lower incidence of sexual intercourse, and fewer sexual partners. They also reported more commitment and attachment to school, better academic achievement, and less school misbehavior. The late intervention students did not differ significantly from the control group in health risk behaviors. Hawkins, J.D., Catalano, R.F., Kosterman, R., Abbott, R., and Hill, K.G. Preventing Adolescent Health-Risk Behaviors by Strengthening Protection during Childhood. Archives of Pediatric and Adolescent Medicine, 153, pp. 226-234, 1999.

Sex Behavior and Substance Use Among Young Adults

The relationship between substance use during adolescence and HIV risk behavior among young adults aged 19-21 years with and without a college education was examined. Subjects were part of a longitudinal study that measured drug use and other variables in 6th-10th grades. Subjects who participated in at least 3 of these data collection periods were the targeted sample for the present study (N=952). Results indicate that increased use of alcohol and marijuana at younger ages is related to riskier sexual activity and increased use of alcohol and marijuana as young adults. Staton, M., Leukefeld, C., Logan, T. K., Zimmerman, R., Lynam, D., Milich, R., Martin, C., McClanahan, K., and Clayton, R.R. Risky Sex Behavior and Substance Use Among Young Adults. Health & Social Work, 24, pp. 147-154, 1999.

The Impact of Parental AIDS on Adolescent Children

This study examines the problem of adolescent children taking on adult parenting and spousal roles in families where a parent has AIDS (PWA). In Phase 1, relationships among parental AIDS-related illness, parent drug use, parent and adolescent demographics, and parentification indicators (parental, spousal, or adult role-taking) were assessed among 183 adolescent-parent pairs (adolescents aged 11-18 yrs). Adult role-taking was associated with maternal PWAs, female adolescents, and greater parent drug use. Greater parental AIDS-related illness predicted more spousal and parental role-taking. Parent drug use predicted more parental role-taking by adolescents. In Phase 2, the impact of parentification on later adolescent psychological adjustment was examined in 152 adolescents. Adult role-taking predicted more internalized emotional distress; parental role taking predicted externalized problem behaviors such as sexual behavior, alcohol and marijuana use, and conduct problems. Given these dysfunctional outcomes, interventions to mitigate parentification among children of PWAs was discussed. Stein, J.A., Riedel, M., and Rotheram-Borus, M.J. Parentification and its Impact on Adolescent Children of Parents with AIDS. Family Process, 38, pp. 193-208, 1999.

Problem Behavior of Adolescents Whose Parents Have AIDS

Substance use, acts of sexual risk, conduct problems, and internalizing, externalizing, and somaticizing mental health symptoms were examined among 239 adolescents (aged 11-19 yrs) and their parents living with AIDS in New York City. The assessment measures administered were constructs emerging from the creation of latent variables using a structural equational modeling approach. Other factors assessed were parental illicit drug use, health status, and internalizing of emotional distress, as well as adolescent alcohol and marijuana use. Consistent with theories regarding imitative behavior, stress, and anticipatory loss, adolescents' externalizing behavior problems and somatic symptoms were related to their parents' status. Rotheram-Borus, M.J., and Stein, J. A. Problem Behavior of Adolescents whose Parents are Living with AIDS. American Journal of Orthopsychiatry, 69, pp. 228-239, 1999.

Youth Living With HIV as Peer Leaders

Community-based service providers often hire youth living with HIV (YLH) as peer leaders or facilitators for delivering

HIV education to uninfected adolescents. Life narratives were collected from 44 YLH during a hypotheses-generating 2-yr ethnographic study. About 30% of the youth were employed as peer educators. While 60% of the 44 youth had lower-class backgrounds, only 23% of the peer leaders were lower class. One-fifth of the sample was female, but more than one-half of the peer leaders were female. After identifying and categorizing difficulties experienced by the peer leaders, a frequency count of each theme was conducted. Issues about professional boundaries were evident in 38.5% of the youth's narratives, indicating conflicts in their roles as peer leaders; 23% of the youth engaged in substance use and sexual behaviors that placed themselves and uninfected youth in their peer educator programs at risk; and 8% of the youth reported relapse while peer leaders. These data suggest reconsideration or restructuring of existing peer education models that employ YLH. Luna, G.C., and Rotheram-Borus, M.J. Youth Living with HIV as Peer Leaders. American Journal of Community Psychology, 27, pp. 1-23, 1999.

An Institutional Analysis of HIV Prevention Efforts by the Nation's Outpatient Drug Abuse Treatment Units

Drawing from an institutional-theory perspective on innovations in organizations, this research examines human immunodeficiency virus (HIV) prevention practices by the nation's outpatient substance abuse treatment units during the period from 1988 to 1995. An institutional perspective argues that organizations adopt new practices not only for technical reasons, but also because external actors actively promote or model the use of particular practices. The extent to which treatment units use several practices to prevent HIV infection among their clients and among drug-users not in treatment are examined. Results from random-effects regression analyses of national survey data show that treatment units significantly increased their use of HIV prevention practices from 1988 to 1995. Further, the results show that treatment units' use of prevention practices was related to clients' risk for HIV infection, unit resources available to support these practices, and organizational support for the practices. Implications are discussed for an institutional view of organizational innovation as well as for research on HIV prevention. D'Aunno T., Vaughn T.E., and McElroy P. Journal of Health and Social Behavior, 40(2), pp. 175-192, June 1999.

Changes in HIV-related Risk Behaviors Following Drug Abuse Treatment

This study measures changes in HIV-related injection drug and sexual risk behaviors following drug treatment in a therapeutic community program. A prospective cohort study of 261 drug users, randomly assigned to day or residential treatment, were interviewed 2 weeks after entering treatment and 6, 12, and 18 months later (follow-up rate: 83%). Drug abuse treatment was associated with a decrease in HIV-related risk behavior. Greater reductions in injection risk behaviors were associated with more time in treatment and being in the later waves of interviews. Interview wave was also associated with greater reductions in sexual risk behavior. Woods, W.J., Guydish, J.R., Sorensen, J.L., Coutts, A., Bostrom, A., and Acampora, A. AIDS, 13, pp. 2151-2155, 1999.

HIV Testing in Substance Abusers

Which drug abuse treatment patients are HIV tested is a significant public and individual health issues in need of further examination. Over 15 months in 1992 and 1993, interview data gathered from 2315 patients at entry to treatment were analyzed to examine factors associated with previous HIV testing. Among this group of alcohol, heroin, and cocaine abusers, 53% (1231) reported previous HIV testing. Although those with identifiable HIV risk factors were more likely to have been tested, 27% of injection drug users, 38% with multiple sexual partners, 39% of those with a history of a sexually transmitted disease, and 38% of those with previous drug treatment had not been HIV tested. Other factors associated with previous HIV testing included having a primary care physician, the primary care physician's awareness of the patient's substance abuse problem, and having received prior addiction care. Of those tested, 10% (n = 122) reported a positive test, and 7% (n = 81) had not received the test results. Of those with positive test results, 37% were not injection drug users. Promotion of HIV testing among alcohol and other drug abusers in both medical and substance abuse treatment settings should be a priority. Samet, J.H., Mulvey, K.P., Zaremba, N., and Plough, A. Am J Drug Alcohol Abuse, 25(2), pp. 269-280, May 1999.

Differential Access to HIV Services Linked to HIV Transmission Mode in Urban Poor

Researchers examined the effect of HIV-health status and HIV transmission mode on access to HIV-related services among African American, Hispanic, and White HIV+ persons in Houston. Data were collected from 169 African Americans, 72 Hispanics, and 253 White HIV+ persons seeking social and medical services at community-based organizations. A total of 42 logistic regressions were estimated for each HIV service and ethnic group. The results showed significant differences in access to HIV social services based on HIV transmission mode among the three racial/ethnic groups. However, no differences were found in access to HIV medical services based on either HIV status or HIV-transmission mode among the three racial/ethnic groups. Montoya, I., Trevino, R., and Kreitz, D. Access to HIV Services by the Urban Poor. J Community Health, 24(5), pp. 331-346, 1999.

Heating Drug Solutions May Inactivate HIV-1

An ethnographic research study was conducted in response to concerns about risk of HIV-1 transmission from drug injection paraphernalia such as cookers. Specifically, ethnographic methods were used to develop a descriptive typology of the paraphernalia and practices used to prepare and inject illegal drugs. Observational data were then applied in laboratory studies in which a quantitative HIV-1 micro culture assay was used to measure the recovery of infectious HIV-1 in cookers. HIV-1 survival inside cookers was a function of the temperature achieved during preparation of drug solution; HIV-1 was inactivated once temperature exceeded, on average, 65 degrees centigrade. Although different types of cookers, volumes, and heat sources affected survival times, heating cookers 15 seconds or longer reduced viable HIV-1 below detectable levels. Clatts, M., Heimer, R., Abdala, N., Goldsamt, L., Sotheran, J., Anderson, K., Gallo, T., Luciano, P., and Kyriakides, T. HIV-1 Transmission in Injection Paraphernalia: Heating Drug Solutions May Inactivate HIV-1. JAIDS, 22(2), pp. 194-199, 1999.

Nitrites and Kaposi's Sarcoma in AIDS Subjects

This group has been studying the effects of nitrites on immune processes. In a correlative study, they have associated nitrite exposure with tumor production in mice. Epidemiological studies have correlated the incidence of Kaposi's sarcoma (KS) in AIDS with a history of abuse of nitrite inhalants. To determine if exposure to nitrite inhalants could alter tumor growth, syngeneic PYB6 tumor cells were injected into groups of mice. Exposure of these mice to inhaled isobutyl nitrite increased both the tumor incidence and the tumor growth rate by almost 4-fold. Following only five daily exposures to the inhalant, the induction of specific T cell mediated cytotoxicity was inhibited by 36%. Similar inhalation exposures inhibited the tumoricidal activity of activated macrophages by 86%. The data suggest that exposure to abused levels of a nitrite inhalant compromised tumor surveillance mechanisms. Soderberg, L.S.F., Toxicology Letters, 104, pp. 35-41, 1999.

Marijuana Withdrawal Among Adults Seeking Treatment for Marijuana Dependence

The clinical relevance of marijuana withdrawal has not been established. Budney et al. has documented for the first time, the incidence and severity of perceived marijuana withdrawal symptoms in a clinical sample of 54 marijuana-dependent adults (average age, 33.8+8 years; 15% women) seeking outpatient treatment for marijuana dependence. Eighty-two percent of the subjects smoked marijuana 4+ times daily, and approximately 54% smoked 26+ cigarettes daily. The subjects completed a 22-item Marijuana Withdrawal Symptom checklist based on their most recent period of marijuana abstinence. The majority (57%) indicated that they had experienced > six symptoms of at least moderate severity and 47% experienced > four severe symptoms. Withdrawal severity was greater in those with psychiatric symptomatology and more frequent marijuana use. The authors concluded that this study further provides support for a cluster of withdrawal symptoms experienced following cessation of regular marijuana use and that the effective and behavioral symptoms were consistent with those observed in previous laboratory and interview studies. Furthermore, since withdrawal symptoms are frequently a target for clinical intervention with other substances of abuse, this may also be appropriate for marijuana. Budney, A.J., Novy, P.L., and Hughes, J.R. Marijuana Withdrawal Among Adults Seeking Treatment for Marijuana Dependence, Addiction, 94(9), pp. 1311-1321, 1999.

Marijuana Smoking and Risk of Cancer

Zhang et al. from UCLA conducted a case-control study of 173 previously untreated cases of squamous cell carcinoma of the head and neck; and 176 cancer-free controls at Sloan-Memorial Kettering Cancer Center, New York, between 1992 and 1994. They collected epidemiological data by using a structured questionnaire, which included history of tobacco smoking, alcohol use, and marijuana use. The overall prevalence of lifetime marijuana use was 9.7% in controls and 13.9% in cases. The highest prevalence of marijuana use was found in cases with squamous cell carcinoma of the larynx (n=48; 22.9%) and tongue (n=52; 19.2%). Controlling for age, sex, race, education, alcohol use, and pack-years of cigarette smoking, the risk of head and neck cancer was increased with marijuana use [OR comparing ever with never users, 2.6;95% CI,1.1-6.6] with a dose-response relationships for frequency of marijuana use/day and years of marijuana use (P for trend <0.05). The associations were stronger for subjects who were 55 years of age and younger (OR,3.1;95% CI,1.0-9.7). These data suggest that marijuana use may increase the risk of head and neck cancer with a strong dose-response pattern, and that marijuana use may interact with mutagen sensitivity and other risk factors (cigarette smoking, alcohol use) to increase the risk of head and neck cancer. The researchers stated that these results need to be interpreted with some caution in drawing causal inferences because of certain methodological limitations, especially with regard to interactions mentioned above. Zhang, Z.F., Morgenstern, H., Spitz, M.R., Tashkin, D.P., et al. Marijuana Use and Increased Risk of Squamous Cell Carcinoma of the Head and Neck. Cancer Epidemiology, Biomarkers and Prevention, 8(12), pp. 1071-1078, 1999.

Level of In Utero Cocaine Exposure and Neonatal CNS Ultrasound Findings

Researchers in Boston report ultrasound findings suggestive of an association between vascular injury of the neonatal CNS and level of prenatal cocaine exposure. Three cocaine exposure groups were studied based on maternal report and infant meconium testing: unexposed, heavier cocaine exposure (>75th percentile self-reported days of use or meconium benzoylecognine concentration), and lighter cocaine exposure (all others). Analyses involved neonatal ultrasounds from 241 well, term infants. Infants with lighter cocaine exposure and unexposed infants did not differ on any of the ultrasound results. Infants with heavier cocaine exposure were more likely than unexposed infants to show subependymal hemorrhage in the caudo-thalamic groove (odds ratio of 3.88 with control for gender, gestational age, birth weight, maternal parity, blood pressure in labor, ethnicity, and use of cigarettes, alcohol, and marijuana during pregnancy). The researchers suggest that the inconsistency between these findings and others reported in the literature may reflect previous lack of consideration of possible dose effects. The long-term functional implications of these findings remain to be determined. Children represented in this report continue to be studied as part of an ongoing longitudinal study of development relative to illicit drug exposure in utero. Frank, D.A., McCarten, K.M., Robson, C.D., Mirochnick, M., Cabral, H., Park, H., and Zuckerman, B. Level of In Utero Cocaine Exposure and Neonatal Ultrasound Findings. Pediatrics, 104, pp. 1101-1105, 1999.

[Office of the Director][Report Index][Next Report Section]

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National Institute on Drug Abuse

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

February, 2000

Research Findings

Epidemiology, Etiology and Prevention Research

Ethnographic Study Explores Link Between Non-injecting Heroin Use and Heroin Markets

Ethnographers in New York City explored the shifting dynamics of the retail heroin markets on the Lower East Side, how market conditions affected non-injecting heroin users' routes of administration and patterns of use, and the ways in which non-injecting heroin users adapt to illegal heroin markets experiencing increased attention from law enforcement. Heroin markets have proven to be highly adaptable in response to increased police enforcement activities aimed at controlling the supply of heroin. This adaptability is reflected in the increasing number of heroin users in spite of police surveillance and crackdowns. Two key changes in the heroin markets are linked to the rise in heroin use as law enforcement also had increased: one is an expansion of the market through mobile communication devices (e.g., pagers and cellular phones) and the other is direct retail sales through loosely organized drug networks that provide delivery services for heroin distribution to the suburbs. Changes in the retail heroin market are associated with an increasingly more heterogeneous and dispersed customer base, including many more women who sniff heroin and become intermediates in drug distribution and marketing. Use patterns are "elastic" in response to changes in heroin supply and purity of the drug; occasional users are more likely to stop using when purity declines and supply diminishes, but heavily dependent non-injectors are more likely to transition to injecting drug use to achieve their high. Andrade, X., Sifaneck, S., and Neaigus, A. Dope Sniffers in New York City: An Ethnography of Heroin Markets and Patterns of Use. J Drug Issues, 29(2), pp. 271-298, 1999.

Drug Paraphernalia Laws and Injection-Related Infectious Diseases among IDUs

Drug paraphernalia laws in 47 U.S. states make it illegal for IDUs to possess syringes. Researchers examined the relationship between concern about arrest while carrying drug paraphernalia and injection-related risk behaviors among street-recruited IDUs in Northern California. They found that, of 424 IDUs interviewed, 150 (35%) reported concern about being arrested while carrying drug paraphernalia. In multivariate analysis, IDUs concerned about being arrested were significantly more likely than others to share syringes and injection supplies. The authors argue for a reconsideration of the consequences of drug paraphernalia laws to help IDUs reduce their risks for transmitting blood-borne viruses. Bluthenthal, R., Kral, A., Erringer, E., and Edlin, B. Drug Paraphernalia Laws and Injection-Related Infectious Diseases among Drug Injectors. J Drug Issues, 29(1), pp. 1-16, 1999.

ADHD and Early Drug Use

This study followed a community-based sample of low birth weight and normal birth weight children and their mothers, initially assessed at age 6 and followed up at age 11. Several findings are of note. Both low birth weight and normal birth weight subjects with ADHD (attention deficit hyperactivity disorder) were found to have increased risk of substance use by age 11. However, there was an interaction effect between ADHD and externalizing problems: children with low levels of externalizing problems were at low risk, and children with high levels of externalizing problems were at high risk for drug use, regardless of ADHD status. It was at moderate levels of externalizing problems that children with ADHD demonstrated increased risk for early drug use. Internalizing problems did not

predict early drug use. The risk for drug use did not differ between those children who did or did not receive pharmacotherapy [usually methylphenidate (Ritalin)] as treatment for ADHD. Low parental monitoring and peer drug use were associated with increased risk for early drug use. Maternal history of depression, anxiety disorder, or substance abuse or dependence did not change the relationship between ADHD and children's drug use. Chilcoat, H.D. and Breslau, N. Pathways From ADHD to Early Drug Use. Journal of the American Academy of Child and Adolescent Psychiatry, 38, pp. 1347-1354, 1999.

Childhood Victimization and Drug Abuse: Comparison of Prospective and Retrospective Findings

This study examined whether childhood victimization increases risk for drug abuse using prospective and retrospective victimization information. Substantiated cases of child abuse/neglect from 1967 to 1971 were matched on gender, age, race, and approximate social class with nonabused/nonneglected children and followed prospectively into young adulthood. Between 1989 and 1995, 1,196 participants (676 abused/neglected and 520 control) were administered a 2-hr interview, including measures of self-reported childhood victimization and drug use/abuse (NIMH Diagnostic Interview Schedule--Version III--Revised). Prospectively, abused/neglected individuals were not at increased risk for drug abuse. In contrast, retrospective self-reports of childhood victimization were associated with robust and significant increases in risk for drug abuse. The relationship between childhood victimization and subsequent drug problems is discussed and is more complex than originally anticipated. Widom, C.S., Weiler, B.L., and Cottler, L.B. Childhood Victimization and Drug Abuse: Comparison of Prospective and Retrospective Findings. Journal of Consulting and Clinical Psychology, 67(6), pp. 867-880, 1999.

Smoking Initiation and Escalation in Early Adolescent Minority Girls

The objective of this study was to examine the effectiveness of a drug abuse prevention program in reducing the initiation and escalation of smoking in a sample of predominantly minority 7th grade girls. The 15-session prevention intervention teaches social resistance skills within an intervention designed to promote personal and social competence skills. Smoking rates among girls from 29 New York City public schools who received the program (n=1,278) were compared with those of a control group of girls (n=931). Participants were less likely to initiate smoking compared to controls. There were also significant program effects on smoking intentions, smoking knowledge, perceived peer and adult smoking norms, drug refusal skills, and risk taking. Experimental smokers in the intervention group were less likely to escalate to monthly smoking relative to controls. Botvin, G.J., Griffin, K.W., Diaz, T., Miller, N. and Ifill-Williams, M. Smoking Initiation and Escalation in Early Adolescent Girls: One-Year Follow-Up of a School-Based Prevention Intervention for Minority Youth. Journal of the American Medical Women's Association, 54, pp. 1-6, 1999.

A Six-Year Follow-Up Study of Determinants of Heavy Cigarette Smoking Among High-School Seniors

Most adult cigarette smokers start smoking during adolescence. Few studies, however, have focused on adolescents that are heavy smokers. This study examined the link between risk and protective factors measured during early adolescence and heavy smoking when youth were high-school seniors. As part of a school-based survey, seventh grade students (N=743) reported on experimentation with psychoactive substances and psychosocial factors associated with smoking. By twelfth grade 12% of students (n=88) smoked a pack of cigarettes or more each day. Heavy smoking was predicted by: poor grades, experimentation with cigarettes or alcohol, a mother or many friends that smoke, and risk-taking behaviors in the seventh grade. Anti-smoking attitudes and those of one's parents and friends predicted rates of heavy smoking among girls in high school. Early intervention programs that address the social and psychological determinants of smoking may have important preventive effects in terms of experimental smoking and in later heavy smoking. Thus, prevention efforts that reduce, delay, or prevent early experimentation with smoking may significantly reduce heavy cigarette consumption in later adolescence and adulthood. Griffin, K.W., Botvin, G.J., Doyle, M.M., Diaz, T. and Epstein, J.A. A Six-Year Follow-Up Study of Determinants of Heavy Cigarette Smoking among High-School Seniors. Journal of Behavioral Medicine, 22, pp. 271-284, 1999.

Adverse Effects of Grouping Deviant Youth

Recent research has suggested potential harmful effects of group-based skill training for children and adolescents with externalizing problems. This article reviews four types of evidence from published literature on the role of deviant peers in the socialization of aggressive youth, studies reporting adverse treatment effects for grouped interventions, studies comparing treatment outcomes that differed in the extent to which participants were grouped with deviant peers, and studies that highlight variables that mediate negative treatment outcomes. The review

supports the conclusion that grouping deviant youth in treatment may produce unintended, harmful effects. Arnold, M.E. and Hughes, J.N. First Do No Harm: Adverse Effects of Grouping Deviant Youth for Skills Training. Journal of School Psychology, 37, pp. 99-115, 1999.

10-Year Follow-Up of Project DARE

The present study examined the impact of Project DARE (Drug Abuse Resistance Education), a widespread drug-prevention program, 10 years after administration. A total of 1,002 6th grade students who had either received DARE or a standard drug-education curriculum, were reevaluated at age 20. Few differences were found between the 2 groups in terms of actual drug use, drug attitudes, or self-esteem, and in no case did the DARE group have a more successful outcome than the comparison group. Lynam, D.R., Milich, R., Zimmerman, R., Novak, S.P., Logan, T. K., Martin, C. Leukefeld, C., and Clayton, R.R. Project DARE: No Effects at 10-year Follow-Up. Journal of Consulting & Clinical Psychology, 67, pp. 590-593, 1999.

Early Deviance in the Children of Narcotic Addicts

This descriptive study examined the self-reported behaviors of 285 male and female adolescent children (aged 12-17 yr) of narcotic addicts participating in methadone maintenance programs. These children responded to an 2.5-hour interview questionnaire focusing on current and past activities, including criminal activities prior to age 12. Findings revealed that early deviance, assessed by measures of both severity and variety, was related to current adolescent drug and alcohol use, association with deviant peers, a negative view of home atmosphere, and psychological symptomatology. These results are contrasted with the retrospective reports of adolescent behavior obtained from adult male narcotic addicts in a prior study of vulnerability to addiction. The comparability of study results is discussed in the context of developmental risk factors, prevention and treatment strategies, and other considerations specifically related to the development of children of narcotic addicts. Nurco, D.N., Blatchley, R.J., Hanlon, T.E., and O'Grady, K.E. Early Deviance and Related Risk Factors in the Children of Narcotic Addicts. American Journal of Drug & Alcohol Abuse, 25, 25-45, 1999.

Factors in Drug Use Initiation vs. Misuse in Women

This study applied a novel modeling technique to data from a sample of female twins, to estimate the role of genetic and environmental risk factors influencing initiation and subsequent misuse of illicit substances. A key feature of this approach is the capacity to distinguish between factors influencing initiation and misuse. The results suggest that shared environmental factors have a significant impact on the probability of drug use initiation, but no new influence on the risk for misuse once drug use is initiated. Furthermore, it appears that one set of genetic risk factors influences risk for initiation while another set appears important to the liability for misuse, once drug initiation has occurred. Kendler, K.S., Karkowski, L.M., Corey, L.A., Prescott, C.A., and Neale, M.C. Genetic and Environmental Risk Factors in the Aetiology of Illicit Drug Initiation and Subsequent Misuse in Women. British Journal of Psychiatry, 175, pp. 351-356, 1999.

Substance Use and Abuse in Female Twins

This study reports findings on the relative roles of environmental and genetic factors in the risk for use, abuse, and dependence on hallucinogens, opiates, sedatives, and stimulants; previous reports have already examined factors related to use and abuse of marijuana and cocaine. Results suggest that both genetic and familial factors contribute to twin resemblance for the more common patterns of hallucinogen and stimulant use, while twin resemblance on the less common use of opiates and sedatives as well as stimulant abuse and dependence were solely the result of genetic factors. These findings confirm the strong influence of family factors, including genetic factors, in the vulnerability to illicit substance use and abuse in women. Kendler, K.S., Karkowski, L., and Prescott, C.A. Hallucinogen, Opiate, Sedative and Stimulant Use and Abuse in a Population-based Sample of Female Twins. Acta Psychiatrica Scandinavica, 99, pp. 368-376, 1999.

Peer-Influence Versus Peer-Selection in Adolescent Substance Use

The correlation between individual adolescents' substance use and substance use by members of their peer groups may be explained by direct influence of peers who use substances or by substance-using adolescents' self-selection into groups of peers who are also users. Researchers at Yeshiva University used latent growth analyses to contrast peer-influence and peer-selection as mechanisms accounting for 6th-9th graders' tobacco, alcohol, and marijuana use. Participants were surveyed three times, at one-year intervals, about peers' substance use and their own use; Sample 1 had 1,190 participants (initial mean age = 12.4 years), Sample 2 had 1,277 participants (initial mean age = 11.5 years). Latent growth analyses that were based on composite scores indicated that initial peer use was

positively related to rate of change in adolescent use, supporting the influence mechanism; there was little evidence for a selection mechanism. Difficult temperament, poor self-control, and deviance-prone attitudes were related to initial levels for both peer and adolescent use. It is concluded that peer influence is the primary mechanism during middle adolescence. Temperament-related attributes may be predisposing to early experimentation and deviant-peer affiliations. Wills, T.A. and Cleary, S.D. Peer and Adolescent Substance Use Among 6th-9th Graders: Latent Growth Analyses of Influence Versus Selection Mechanisms. Health Psychology, 18(5), pp. 453-463, 1999.

Correlates of Moderate Alcohol Use Versus Problem Alcohol Use

To evaluate the assumption that moderate alcohol use and problem alcohol use represent variations along the same continuum, researchers used a longitudinally ascertained community sample of 15-17-year-old children of alcoholics (COAs) and a demographically matched comparison group (non-COAs) and identified the correlates of adolescent alcohol use and those of problem use. A typology of adolescent alcohol use was created, and alcohol use groups were compared on variables chosen from nine psychosocial domains (parent alcohol use, family functioning, maternal parenting, paternal parenting, stress and emotional distress, peer influences, alcohol expectances, adolescent temperament/personality, and adolescent externalizing symptoms. The correlates of problem alcohol use were different from those of moderate use. Problem use was associated with fundamental family disruptions and poor psychological functioning. In contrast, the determinants of moderate alcohol use reflected unconventionality and socialization specific to alcohol. Few psychosocial variables distinguished abstainers from light drinkers. The findings are consistent with the idea that moderate drinking is associated with a sociocultural context that supports alcohol use while problem alcohol use is associated with psychosocial impairment. This implies that intervention researchers should articulate their outcome of interest and design interventions accordingly; prevention of alcohol problems, for example, might focus on reducing family disruptions and enhancing coping skills, whereas prevention of moderate adolescent drinking might focus on increasing negative expectances about alcohol use and encouraging affiliations with peers who do not use alcohol. Colder, C.R. and Chassin, L. The Psychosocial Characteristics of Alcohol Users Versus Problem Users: Data from a Study of Adolescents at Risk. Development and Psychopathology, 11(2), pp. 321-348, 1999.

Gender Differences in Drug Use Traced to Differences in Opportunity to Use

Researchers at Johns Hopkins University used data from the 1979-1994 National Household Surveys on Drug Abuse to examine whether male-female differences in rates of drug use could be traced back to differences in rates of exposure to initial opportunities to try drugs, rather than to sex differences in the probability of making a transition to use, once opportunity has occurred. Survey respondents were 131,226 US residents aged 12 years and older. The investigators estimated proportion of males and females with an opportunity to use marijuana, cocaine, hallucinogens and heroin; proportions reporting use among those having an opportunity to use each drug; proportion making a "rapid transition" from initial opportunity to initial use. They found that males were more likely than females to have an initial opportunity to use drugs. Once an opportunity had occurred, however, few male-female differences were observed in the probability of making a transition into drug use,. These results suggest that the previously documented male excess in rates of drug use may be due to greater male exposure to opportunities to try drugs, rather than to greater chance of progressing from initial opportunity to actual use. This suggests that sex differences in drug involvement emerge early in the process. Van Etten, M.L., Neumark, Y.D., and Anthony, J.C. Male-Female Differences in the Earliest Stages of Drug Involvement. Addiction, 94(9), pp. 1413-1419, 1999.

Boys' Externalizing Behavior Predicted by Individual Traits and Family Context

Evidence suggests the development of substance abuse is related to prior externalizing behaviors which, in turn, may be related to the temperament traits of parent and child and the quality of the parent-child relationship. These factors may play a mediational role in intergenerational transmission of substance abuse. In research using the CEDAR sample, investigators examined individual traits in a family context to identify processes that account for the relationship between fathers' SUD + status and sons' externalizing behaviors. Results obtained from SUD + (n = 89) and SUD - (n = 139) families show that individual traits, family contextual variables and deviant peer affiliations accounted for 58% of the variance on sons' externalizing behavior scale (EBS) scores. Fathers' abusive propensities toward their sons mediated the relationship between fathers' SUD + status and sons' EBS scores 2 years later. Also, high risk cluster (HRC) and low risk cluster (LRC) memberships were derived from cluster analyses of the continuous risk factor scores that predicted sons' EBS scores. Preliminary relative risk ratios show that sons classified into the HRC at age 10-12 were at greater risk for DSM-III-R conduct disorder and SUD outcomes at age 16 than sons assigned to the LRC, SUD + or SUD - groups. The results support the notion of an ontogenetic pathway to externalizing behavior problems that may be prodromal to CD and SUD outcomes and suggest the need for family-based prevention programs to that take account of family members' temperament traits and abusive propensities of parents toward their offspring in order to reduce the risk of CD and SUD outcomes. Blackson, T.C., Butler, T., Belsky,

J., Ammerman, R.T., Shaw, D.S., and Tarter, R.E. Individual Traits and Family Contexts Predict Sons' Externalizing Behavior and Preliminary Relative Risk Ratios for Conduct Disorder and Substance Use Disorder Outcomes. Drug and Alcohol Dependence, 56(2), pp. 115-131, 1999.

The Epidemiology of Alcohol, Tobacco, and Other Drug Use Among Black Youth

This study examined the patterns, trends, and sociodemographic correlates of alcohol, tobacco, and other drug use within the black youth population. The data indicate that the drug most prevalent among black secondary students is alcohol, followed by tobacco and marijuana. By twelfth grade, 7 in 10 black secondary students have used alcohol, less than 50 percent have smoked cigarettes, 25 percent have used marijuana, and less than 2 percent have used cocaine. Trend data indicate that there were significant declines in drug use among black (and other) youth throughout the 1980s, but tobacco, alcohol, and marijuana have been on the increase throughout the 1990s. Data on the sociodemographic correlates of black students' drug use reveal that levels of substance use are, on average, higher among males than females and among students who do not live with either of their parents than among those who live with one or both parents. Although there is a trend toward lower levels of drug use among youth as parents' level of education increases, the relationship varies across drugs and grade level. The relationship between urbanicity and drug use varies considerably by drug. Finally, cigarette use is highest in the Northeast followed by the North Central region, the South, and the West; alcohol use is highest in the North Central region; and marijuana and cocaine prevalence rates vary by region, with use generally being lowest in the South. Wallace, J.M., Jr., Forman, T.A., Guthrie, B.J., Bachman, J.G., O'Malley, P.M., and Johnston, L.D. The Epidemiology of Alcohol, Tobacco and Other Drug Use among Black Youth. Journal of Studies on Alcohol, 60(6), pp. 800-809, 1999.

Social Influences on Adolescent Problem Behavior

The social context model of development of adolescent antisocial behavior advanced by G. R. Patterson et al. (1992) appears to generalize the development of a diverse set of problem behaviors. Structural equation modeling methods were applied to 18-month longitudinal data from 523 14-17 yr old adolescents. The problem behavior construct included substance use, antisocial behavior, academic failure, and risky sexual behavior. Families with high levels of conflict were less likely to have high levels of parent-child involvement. Such family conditions resulted in less adequate parental monitoring of adolescent behavior, making associations with deviant peers more likely. Poor parental monitoring and associations with deviant peers accounted for 46% of the variance in engagement in problem behavior. Although association with deviant peers was the most proximal social influence on problem behavior, parental monitoring and family factors (conflict and involvement) were key parenting practices that influenced this developmental process. Ary, D.V., Duncan, T.E., Biglan, A. Metzler, C.W., Noell, J.W., and Smolkowski, K. Development of Adolescent Problem Behavior. Journal of Abnormal Child Psych, 27, pp. 141-150, 1999.

Delaying Onset and Progression of Adolescent Substance Abuse

This study examined the effects of the Iowa Strengthening Families Program (ISFP) and the Preparing for the Drug Free Years Program (PDFY) on young adolescent transitions from nonuse of substances to initiation and progression of substance use. Analyses incorporated three waves of data collected over a 2_-year period from 329 rural young adolescents. Outcomes were analyzed by using log linear models that incorporated substance use status frequencies derived from latent transition analyses. Effects on delayed substance use initiation were shown for both the ISFP and PDFY at a two-year follow-up. Also at this follow-up, the PDFY showed effects on delayed progression of use among those previously reporting initiation. Spoth, R., Reyes, M. L., Redmond, C., and Shin, C. Assessing a Public Health Approach to Delay Onset and Progression of Adolescent Substance Use: Latent Transition and Log Linear Analyses of Longitudinal Family Preventive Intervention Outcomes. Journal of Consulting and Clinical Psychology, 67, pp. 619-630, 1999.

Primary Socialization Theory: Drug Use and Deviance

In a series of five articles, Oetting and colleagues present primary socialization theory. The theory proposes that drug use and deviant behaviors emerge from interactions with primary socialization sources-the family, the school, and peer clusters. Each of these sources can transmit either pro-social or deviant norms. Cultural norms for substance use are transmitted through interactions and can differ across cultures; in some, substance use is culturally required, in others tolerated, and in others sanctioned. Therefore, ethnicity and cultural identification do relate to substance use. Individual personality characteristics and traits however, are not found to directly relate to drug use and deviance. Rather, in nearly all cases they influence outcomes through interactions between the individual and the primary socialization sources. The theory develops a parsimonious explanation of how characteristics of both the local community and the larger extended community influence drug use and deviance. Oetting, E.R. & Donnermeyer, J.F. Primary Socialization Theory: The Etiology of Drug Use and Deviance I, Substance Use & Misuse, 33,(4) pp. 995-

1026, 1998.; Oetting, E.R., Deffenbacher, J.L., & Donnermeyer, J.F., Primary Socialization Theory. The Role Played by Personal Traits in the Etiology of Drug Use and Deviance II, Substance Use & Misuse, 33(6) pp. 1337-1366, 1998.; Oetting, E.R., Donnermeyer, J.F., & Deffenbacher, J.L. Primary Socialization Theory: The Influence of the Community on Drug Use and Deviance III, Substance Use & Misuse, 33(8), pp.1629-1665, 1998.; Oetting, E.R., Donnermeyer, J.F., Trimble, J.E., & Beauvais, F. Primary Socialization Theory: Culture, Ethnicity, and Cultural Identification the Links between Culture and Substance Use IV, Substance Use & Misuse, 33(10), pp. 2075-2107, 1998.;Oetting, E.R. Primary Socialization Theory: Developmental Stages, Spiritually, Government Institutions, Sensation Seeking, and Theoretical Implications V, Substance Use & Misuse, 34(7), pp. 947-982, 1999.

Younger Sibling Drug Use

The purpose of this study was to examine older brother correlates of younger brother drug use in the context of parental influences and younger brother personality. The sample consisted of 278 White male college students and their oldest brothers, who volunteered to answer self-administered questionnaires. Results indicated that 3 domains of influence each had an independent impact on younger brother drug use: (a) parent-younger brother relationships and parent drug use, (b) older brother-younger brother relationships and older brother drug use, and (c) younger brother personality. Modeling of nondrug use and a strong attachment relationship in the parent-younger brother and sibling dyads, as well as younger sibling traits of conventionality, had strong links to low younger brother drug use. Our findings highlight the importance of modeling and mutual parent-child attachment relationships as well as sibling relationships as they relate to the possible etiology of drug use. Brook, J.S., Brook, D.W., and Whiteman, M. Older Sibling Correlates of Younger Sibling Drug Use in the Context of Parent-Child Relations. Genet Soc Gen Psychol Monogr, 125(4), pp. 451-68, 1999.

Substance Abuse and Personality Disorders in Adolescence and Risk of Major Mental Disorders and Suicidality During Adulthood

A community-based longitudinal study was conducted to investigate whether personality disorders (PDs) during adolescence increase the risk for Axis I psychiatric disorders and suicidality during early adulthood. Psychosocial and psychiatric interviews were administered to a representative community sample of 717 youths and their mothers from 2 counties in the state of New York in 1975, 1983, 1985-1986, and 1991-1993. Anxiety, disruptive, eating, mood, personality, and substance use disorders and suicidal ideation and behavior were assessed in 1983 and 1985-1986, when the participants were adolescents, and in 1991-1993, when they were young adults. Adolescents with PDs were more than twice as likely as those without PDs to have anxiety, disruptive, mood, and substance use disorders during early adulthood. These associations remained statistically significant after co-occurring Axis I disorders during adolescence were controlled statistically. Cluster A, B, and C PDs and DSM-IV Appendix B PDs during adolescence were all associated with elevated risk for Axis I disorders during early adulthood after co-occurring Axis I and Axis II disorders during adolescence were controlled statistically. Cluster C PDs during adolescence were associated with elevated risk for suicidal ideation or behavior during early adulthood after co-occurring psychiatric disorders and suicidality during adolescence were controlled statistically. The authors concluded that adolescents in the community with personality disorders are at elevated risk for major mental disorders and suicidal ideation or behavior during early adulthood. This increase in risk is not accounted for by co-occurring Axis I disorders or suicidality during adolescence. Johnson, J.G., Cohen, P., Skodol, A.E., Oldham, J.M., Kasen, S., and Brook, J.S. Personality Disorders in Adolescence and Risk of Major Mental Disorders and Suicidality During Adulthood. Archives of General Psychiatry, 56(9), pp. 805-811, 1999.

Psychiatric Comorbidity Among Adolescents

This study analyzed rates of comorbid psychiatric disorders among adolescents with substance use disorders (SUD) in a community-based sample from the MECA (Methods for the Epidemiology of Child and Adolescent Mental Disorders) Study, and compared the results with findings from other community-based studies of adolescents and adults. Diagnoses were established using the DISC. Three quarters of the subjects with an SUD had a comorbid anxiety, mood or disruptive behavior disorder, compared with one quarter of adolescents without SUD. The relationship with disruptive behavior disorder was the strongest and remained significant after controlling for other co-occurring disorders. Rates of comorbidity were comparable with those found in other studies of adolescents and adults, including some studies of adolescent treatment populations. The cross-sectional data did not shed light on sequence of development of the disorders. Kandel, D.B., Johnson, J.G., Bird, H.R., Weissman, M.M., Goodman, S.H., Lahey, B.B., Regier, D.A., and Schwab-Stone, M.E. Psychiatric Comorbidity Among Adolescents With Substance Use Disorders: Findings From the MECA Study. Journal of the American Academy of Child and Adolescent Psychiatry, 38, pp. 693-699, 1999.

Substance Use Disorders in Youth with Bipolar Disorder

This study uses a new sample to further investigate the relationships between youth bipolar disorder and adolescent substance use disorder (SUD). Youth with adolescent-onset bipolar disorder were at significantly greater risk for SUD than were those with child-onset bipolar disorder, even when controlling for conduct disorder. The findings again suggest that adolescent-onset bipolar disorder is an independent risk factor for SUD meriting further investigation. Wilens, T.E., Biederman, J., Millstein, R.B., Wozniak, J., Hahesy, A.L., and Spencer, T.J. Risk for Substance Use Disorders in Youths With Child- and Adolescent-Onset Bipolar Disorder. Journal of the American Academy of Child and Adolescent Psychiatry, 38, pp. 680-685, 1999.

Effects of Adoption Agency Disclosure on Gene-Environment Interaction

This study tested for potential biasing effects of open adoption on studies of gene-environment interaction. For several of the analyses, parent knowledge of the physical or psychiatric/medical history of the biologic parents interacted with biologic risk for alcoholism or antisocial personality in predicting adoptee outcomes on various behavioral measures. As a retrospective study, the findings could not distinguish the direction of the effect; that is, whether parents with difficult children sought further information about biological risk, or whether the knowledge of risk influenced parenting, perception, or recall. In any case, the findings suggest that adoption studies of gene-environment interaction need to take into account the possibility of bias resulting from openness. Further research may also be indicated to examine the results of open adoption on child outcomes. Riggins-Caspers, K., Cadoret, R.J., Panak, W., Lempers, J.D., Troughton, E., and Stewart, M.A. Gene x Environment Interaction and the Moderating Effect of Adoption Agency Disclosure on Estimating Genetic Effects. Personality and Individual Differences, 27, pp. 357-380, 1999.

Girls' Smoking Influenced More By Parents but Boys' Smoking Influenced More By Peers

In a study of the effects of parental and peer approval of smoking on adolescent smokers' current levels of cigarette use, researchers analyzed data for 913 California 7th-grade students who had previously initiated cigarette use. They applied a Poisson random-effects regression model to examine the number of cigarettes smoked in the past month as a function of race/ethnicity, gender, number of friends approving smoking, and parental approval. Results show a clear correlation between level of smoking and extent of peer and parental approval. However, a stronger relationship between parental approval of smoking and current level of smoking was found for female adolescents than for male adolescents. Conversely, a stronger relationship between peer approval of smoking and current level of smoking was found for male adolescents than for female adolescents. With respect to race, the influence of parental approval of smoking on adolescents' current level of smoking was generally more pronounced for minority adolescents, relative to white adolescents. However, the influence of peer approval of smoking on current level of smoking was strongest for white adolescents and was less strong for black, Hispanic, and Asian adolescents. The findings suggest that smoking cessation programs among adolescents may need to target both parent and peer influences, but these influences may vary by gender and race/ethnicity. Siddiqui, O., Mott, J., Anderson, T., and Flay, B. The Application of Poisson Random-Effects Regression Models to the Analyses of Adolescents' Current Level of Smoking. Preventive Medicine, 29(2), pp. 92-101, 1999.

Predictors of Adolescent Use of Illicit Drugs Other Than Marijuana

Researchers at RAND used multivariate techniques to identify Grade 10 predictors of illicit drug use other than marijuana in Grade 12. A broad range of environmental and personal predictor variables were examined to determine whether social bonds play a protective role and whether certain social bonds have a greater importance for some racial/ethnic groups. The 4,070 subjects in the study sample were drawn from the RAND Adolescent Panel Study that followed adolescents originally drawn from 30 middle schools in eight California and Oregon communities that included urban, suburban, and rural environments. The study population was 75% non-Hispanic Whites, 8% African-Americans, 8% Mexican-Americans, and 9% Asian-Americans. Bonds with family were inversely related to any use of illicit drugs other than marijuana. Prior drug use, especially problem use of "gateway" substances and prior "hard" drug use, were positively related to both any and frequent use. However, variables other than social bonds and prior use were equal to or stronger predictors of both outcomes. African-Americans were less likely to use illicit drugs other than marijuana. Mexican-Americans were more affected by family factors than other groups. Asian-Americans were more affected by school failure. Most predictors of frequent use also presage any use, suggesting that successful efforts to prevent the onset of "hard" drug use should also curb its escalation. Ellickson, P.L., Collins, R.L., and Bell, R.M. Adolescent Use of Illicit Drugs Other Than Marijuana: How Important Is Social Bonding and for Which Ethnic Groups? Substance Use and Misuse, 34(3), pp. 317-346, 1999.

Influence of Child and Adolescent Psychiatric Disorders on Young Adult Personality Disorder

This study examines associations between childhood psychopathology and young adult personality disorder in a random sample of 551 youths, who were 9 to 16 years old at first assessment. Subjects were evaluated for DSM-III-R psychiatric disorders. Information was obtained prospectively from youths and their mothers at three points over 10 years. The predictive effects of prior axis I disorders and adolescent axis II personality disorder clusters A, B, and C on young adult personality disorder were examined in logistic regression analyses. The odds of young adult personality disorder increased given an adolescent personality disorder in the same cluster. Prior disruptive disorders, anxiety disorders, and major depression all significantly increased the odds of young adult personality disorder independent of an adolescent personality disorder. In addition, comorbidity of axis I and axis II disorders heightened the odds of young adult personality disorder relative to the odds of a disorder on a single axis. In conclusion, assessment of personality pathology before late adolescence may be warranted. Childhood or adolescent axis I disorders may set in motion a chain of maladaptive behaviors and environmental responses that foster more persistent psychopathology over time. Identification and treatment of childhood disorders may help to reduce that risk. Kasen, S., Cohen, P., Skodol, A.E., Johnson, J.G., and Brook, J.S. Influence of Child and Adolescent Psychiatric Disorders on Young Adult Personality Disorder. Am J Psychiatry, 156(10), pp. 1529-1535, 1999.

Developmental Trends for Adolescent Substance Use Linked with those for Risky Sexual Behavior

Researchers at the Oregon Research Institute examined associations between the development of adolescent alcohol, cigarette, and marijuana use and risky sexual behavior over time, using latent growth modeling methodology. Gender differences in the development and relationships between use of substances and risky sexual behavior were also examined. Participants were 257 adolescents (mean age = 15.96 years) assessed at three time points over an 18-month period. The intercepts of marijuana with cigarettes and alcohol, and all three substances with risky sexual behavior were significantly related. Development of the three substances showed similar patterns and development of cigarette use covaried with development of risky sexual behavior. There were no significant differences for boys and girls in these relationships. Results are discussed in relation to the need for greater understanding of nonsexual and sex-related problem behaviors and for analyses examining development and change in these behaviors during adolescence. Duncan, S.C., Strycker, L.A., and Duncan, T.E. Exploring Associations in Developmental Trends of Adolescent Substance Use and Risky Sexual Behavior in a High-Risk Population. Journal of Behavioral Medicine, 22(1), pp. 21-34, 1999.

Cigarette and Smokeless Tobacco Use Among Minority Youth

Increases in smoking/tobacco-related diseases among the Hispanic population call for an examination of its use among this population. This study examined the relationship between gender, cultural identification, migrant status, and grade level and the use of tobacco and perception of harmfulness among Mexican American youth. Results showed that when grade, cultural identification, and migrant status of parents was held constant, males more likely to use cigarettes (occasional and daily) and smokeless tobacco than females. No gender effect was found for lifetime cigarette use. The odds of using cigarettes and smokeless tobacco increase substantially across grades. Effects were found for Mexican American/Spanish and Anglo/White American cultural identification and daily cigarette use. Youths who belonged to nonmigrant families or who identified with a traditional Mexican American/Spanish culture were more likely to consider regular tobacco use harmful. Casas, J.M., Bimbela, A., Corral, C.V., Yanez, I., Swaim, R.C., Wayman, J.C., and Bates, S. Cigarette and Smokeless Tobacco Use among Migrant and Nonmigrant Mexican American Youth. Hispanic Journal of Behavioral Sciences, 20, pp. 102-121, 1998.

Assessing the Benefits of Attending a Parenting Skills Program

Using a theoretical model to ground this investigation, hypotheses about factors that moderate the benefits of attending the Preparing for the Drug Free Years (PDFY) program were tested. PDFY is a skills-training program designed to teach parents and children skills that reduce a child's risk for drug and alcohol use. It was hypothesized that high levels of family stress (i.e., marital difficulties or financial concerns) reduce the benefits of program attendance, and that strong pre-program skills (i.e., parental communication, parental negativity, or parent-child relationship quality) increase the benefits of program attendance. These hypotheses were tested on a sample of families that each included a sixth or seventh grade child. The results for fathers (N = 144) supported the study hypotheses, while mothers (N = 150) who benefited most from the program showed the weakest pre-program communication skills and reported the greatest marital difficulties. Rueter, M.A., Conger, R.D., and Mikler, S. Assessing the Benefits of Attending a Parenting Skills Program: A Theoretical Approach to Predicting Direct and Moderating Effects. Family Relations, 48, pp. 67-77, 1999.

Variations in Risk and Protective Factors for American Indian Adolescents

High levels of social stress are related to behavior problems in both Caucasian and American Indian adolescent boys, while high levels of self/family-concept are related to less problem behavior in both groups when using self-report. In contrast, teacher report models indicated that negative life events were the only significant predictor of perceived problem behavior in American Indian boys. For Caucasian males a low self/family-concept predicted teachers' perceptions of problematic behavior. For females, negative events predicted self-reported problem behaviors in American Indians while both negative events and positive self/family-concept contributed significantly for Caucasians. This pattern remained the same when using teacher reports of female problem behaviors. Interventions must address the discrepancy between self and teacher report and the increased likelihood of teachers' observing problematic behaviors in male adolescents. Fisher, P.A., Storck, M., and Bacon, J.G. In the Eye of the Beholder: Risk and Protective Factors in Rural American Indian and Caucasian Adolescents. American Journal of Orthopsychiatry, 69, pp. 294-304, 1999.

Association between Substance Abuse Treatment and Cigarette Use

The influence of risk-behavior bias, drug use, prior cigarette use, and prior and current participation in drug treatment on cigarette use was analyzed using a 3-wave survey of 346 drug abusers. Participation in drug treatment and a risk-behavior bias were hypothesized to predict greater cigarette use. After controlling for prior levels of cigarette use with a longitudinal path model, it was found that participation in drug treatment at Wave 2 significantly predicted increased cigarette use at Wave 2. There were similar results at Wave 3. Additional analyses indicated that reduced heroin use was especially associated with more smoking. Risk-behavior bias predicted more drug and cigarette use and predicted less participation in drug treatment at Wave 3. These results suggest that drug treatment, reduced heroin use, and a tendency toward risky behavior may lead to increased cigarette use, which may represent a form of substance replacement. Conner, B.T., Stein, J.A., Longshore, D., and Stacy, A.W. Associations Between Drug Abuse Treatment and Cigarette Use: Evidence of Substance Replacement. Experimental Clinical Psychopharmacology, 7(1), pp. 64-71, Feb 1999.

Developmental Differences in Beliefs About How Alcohol and Cocaine Affect Behavior

This study examines age group differences in children's knowledge and understanding of how drugs affect behavior. African-American and White children ages 5-7, 8-10, 11-14 years, and a comparison group of college students were asked about alcohol and cocaine. In descriptions of the routes drugs take in the body, mention of gastrointestinal sites decreased across age groups for cocaine but increased for alcohol; mention of vital organs peaked among 8 to 10 year olds; emphasis on peripheral body parts decreased across age groups; and emphasis on blood and brain increased. Knowledge of key elements of a physiological theory of how drugs affect behavior was greater among college students than among younger children. Understanding (causal complexity of explanations) increased with age for cocaine, though not for alcohol. Knowledge and understanding were moderately correlated, suggesting that they represent distinct aspects of thinking about drugs. This study provides data about when children come to know about and understand the effects of drugs. It suggests that younger children think at a more concrete level. They understand that drugs damage the body but are unable to provide coherent and specific physiological explanations of what happens. Sigelman, C.K., Alyson S., Goldberg, F., Davies, E.P., Dwyer, K.M., Leach, D. and Mack, K. Developmental Differences in Beliefs about How Alcohol and Cocaine Affect Behavior. Journal of Applied Developmental Psychology, 20, pp. 1-18, 1999.

Physician Substance Use by Medical Specialty

Self-reported past year use of alcohol, tobacco, marijuana, cocaine, and two controlled prescription substances (opiates, benzodiazepines); and self-reported lifetime substance abuse or dependence was estimated and compared for 12 specialties among 5,426 physicians participating in an anonymous mailed survey. Logistic regression models controlled for demographic and other characteristics that might explain observed specialty differences. Emergency medicine physicians used more illicit drugs. Psychiatrists used more benzodiazepines. Comparatively, pediatricians had overall low rates of use, as did surgeons, except for tobacco smoking. Anesthesiologists had higher use only for major opiates. Self-reported substance use disorders (abuse and dependence) were at highest levels among psychiatrists and emergency physicians, and lowest among surgeons. With evidence from studies such as this one, a specialty can organize prevention programs to address patterns of substance use specific to that specialty, the specialty characteristics of its members, and their unique practice environments that may contribute risk of substance abuse and dependence. (The response rate for this mailed survey was 59 percent. Across specialties, the only significant variation in response rate across specialties was 50 percent for internists, a group for whom no extreme prevalence rates were found.) Hughes, P.H., Storr, C.L., Brandenburg, N.A., Baldwin, D.C., Anthony, J.C., and Sheehan, D.V. Physician Substance Use by Medical Specialty, Journal of Addictive Diseases, 18(2), pp. 23-37, 1999.

Association Between Socioeconomic Status and Psychiatric Disorders

Social causation theory and social selection theory have been put forth to explain the finding that low socioeconomic status (SES) is associated with risk for psychiatric disorders. The predictions of both theories were investigated using data from a community-based longitudinal study. Psychosocial interviews were administered to 736 families from 2 counties in New York State in 1975, 1983, 1985-1986, and 1991-1993. Results indicated that (a) low family SES was associated with risk for offspring anxiety, depressive, disruptive, and personality disorders after offspring IQ and parental psychopathology were controlled, and (b) offspring disruptive and substance use disorders were associated with risk for poor educational attainment after offspring IQ and parental psychopathology were controlled. These findings indicate that social causation and social selection processes vary in importance among different categories of psychiatric disorders. Johnson, J.G., Cohen, P., Dohrenwend, B.P., Link, B.G., and Brook, J.S. A Longitudinal Investigation of Social Causation and Social Selection Processes Involved in the Association between Socioeconomic Status and Psychiatric Disorders. J Abnorm Psychol, 108(3), pp. 490-499, 1999.

Influence of the Teacher-Student Relationship on Childhood Conduct Problems: A Prospective Study

The influence of the quality of the teacher-student relationship on children's adjustment and subsequent levels of aggression was examined in a sample of 61 second and third-grade children nominated and rated by teachers as aggressive. The stability of teachers' and children's reports of relationship quality across academic years was in the low to moderate range. Teachers and children showed little agreement in their reports of relationship quality. However, reports of relationship quality in Year 1 (Y1) predicted teacher-rated aggression the following year. Teachers' reports of relationship quality across Y1 and Y2 predicted peer-rated aggression, but not teacher-rated aggression, in Y3. A positive teacher-student relationship was of greatest benefit to children whose mothers reported rejecting parenting histories. Hughes, J.N., Cavell, T. A., and Jackson, T. Influence of the Teacher-Student Relationship on Childhood Conduct Problems: A Prospective Study. Journal of Clinical Child Psychology, 28, pp. 173-184, 1999.

Beliefs Legitimizing Aggression and Deviant Processing of Social Cues

In two studies the authors examined knowledge and social information-processing mechanisms as two distinct sources of influence on child aggression. Data were collected from 387 boys and girls of diverse ethnicity in three successive years. In Study 1, confirmatory factor analyses demonstrated the discriminant validity of the knowledge construct of aggression beliefs and the processing constructs of hostile intent attributions, accessing of aggressive responses, and positive evaluation of aggressive outcomes. In Study 2, structural equation modeling analyses were used to test the mediation hypothesis that aggression beliefs would influence child aggression through the effects of deviant processing. A stronger belief that aggressive retaliation is acceptable predicted more deviant processing 1 year later and more aggression 2 years later. However, this latter effect was substantially accounted for by the intervening effects of deviant processing on aggression. Zelli, A., Dodge, K.A., Lochman, J.E., Laird, R.D., and The Conduct Problems Prevention Research Group. The Distinction Between Beliefs Legitimizing Aggression and Deviant Processing of Social Cues: Testing Measurement Validity and the Hypothesis that Biased Processing Mediates the Effects of Beliefs on Aggression. A Complementary Perspective to Primary Socialization Theory. Social Psychology, 77, pp. 150-166, 1999.

Classifying Aggressive Children

The purpose of this study was to identify clinically relevant subtypes of aggressive children based on measures of children's self-systems and significant others' perceptions of relationship quality. In a sample of aggressive second- and third-graders, a cluster analysis of children's perceptions of support and significant others' (mother, teacher, and peers) perceptions of relationship quality revealed one subgroup in which self- and other-ratings were below the group mean (concordant-negative), one in which ratings were above the sample mean (concordant-positive), and one in which ratings were discrepant (high child-report and low other-report. However, children in the discrepant group were rated as considerably more aggressive and delinquent than those in the two concordant clusters, who did not differ from each other on measures of internalizing and externalizing behaviors. Edens, J.F., Cavell, T.A., and Hughes, J.N. The Self-Systems of Aggressive Children: A Cluster-Analytic Investigation. Journal of Child Psychology & Psychiatry & Allied Disciplines, 40, pp. 441-453, 1999.

Drug Prevention Programming Readiness

An assessment of community readiness for drug use prevention in rural communities indicated that most of these communities were at low stages of readiness. Minority communities were particularly low in readiness, with only 2%

having any functioning drug prevention programs. Rural communities at different levels of readiness required different types of programs to increase readiness, i.e., communities at the no awareness stage require analysis of historical and cultural issues that support tolerance of drug use, those at the denial and vague awareness stages need specific information about local problems, and communities at the preplanning and preparation stages need information about effective programs, program components and strategies, help in identifying resources, and assistance with staff training. In addition, building and maintaining effective prevention efforts requires continued evolution of readiness through the stages of initiation, stabilization, confirmation and expansion, and professionalization. Revised and updated scales and methods for assessing community readiness are provided. Plested, B., Smitham, D.M., Jumper-Thurman, P., Oetting, E.R., and Edwards, R.W. Readiness for Drug Use Prevention in Rural Minority Communities. Substance Use & Misuse, 34, pp. 521-544, 1999.

School-based Support Groups for Adolescents with Addicted Parents

A qualitative pilot study that evaluated a school-based support group for adolescents with addicted parents identified mediator variables that are hypothesized to be important for child outcomes. These include knowledge of the impact of addiction on the family, improved relationships with family and friends, enhanced coping strategies, improved resiliency to chaotic environments and improved scholastic performance. In the next phase of this study a profile of adolescents interested in the support group will be developed and the effectiveness of the support groups will also be assessed. Preliminary analyses with a limited sample have indicated that students not interested in participating in the group are more likely to be male, Hispanic, and have a lower grade point average. Murphy-Parker, D. and Gance-Cleveland, B. Examining the Benefits of a School-Based Support Group for Adolescents who have an Addicted Parent. Substance Misuse Bulletin, 12, pp. 7-8, 1999.

A Conceptual Framework to Explain Race Differences in Drug Use

Based upon a study that investigated the influence of race and religion on drug use among Black and White youth conducted by researchers at the University of Michigan, a theoretical framework for explaining variations in drug use between the two racial groups has been proposed. Despite a growing literature on race differences in drug use, few studies have offered theoretical explanations for their existence. The central argument advanced by the investigator of this study is that in order for researchers to understand race differences in drug use outcomes, developmental processes, and mean level differences of antecedent influences on drug use, they must understand the ways in which social systems influence individual, interpersonal, and community risk and protective mechanisms that are linked to race and that, in turn, are responsible for racial variation in drug use. Wallace, J.M. Jr., Explaining Race Differences in Adolescent and Young Drug Use: The Role of Racialized Social Systems, Drugs and Society, 14 (1/2), pp. 21-36, 1999.

Impact of Early Adolescent Marijuana Use On Late Adolescent Problem Behaviors

The purpose of this study was to assess the impact of early adolescent marijuana use on late adolescent problem behaviors, drug-related attitudes, drug problems, and sibling and peer problem behavior. African American (n = 627) and Puerto Rican (n = 555) youths completed questionnaires in their classrooms initially and were individually interviewed 5 years later. Logistic regression analysis estimated increases in the risk of behaviors or attitudes in late adolescence associated with more frequent marijuana use in early adolescence. Early adolescent marijuana use increased the risk in late adolescence of not graduating from high school; delinquency; having multiple sexual partners; not always using condoms; perceiving drugs as not harmful; having problems with cigarettes, alcohol, and marijuana; and having more friends who exhibit deviant behavior. These relations were maintained with controls for age, sex, ethnicity, and, when available, earlier psychosocial measures. Early adolescent marijuana use is related to later adolescent problems that limit the acquisition of skills necessary for employment and heighten the risks of contracting HIV and abusing legal and illegal substances. Hence, assessments of and treatments for adolescent marijuana use need to be incorporated in clinical practice. Brook, J.S., Balka, E.B., and Whiteman, M. The Risks for Late Adolescence of Early Adolescent Marijuana Use. Am J Public Health, 89(10), pp. 1549-1554, 1999.

[Office of the Director][Report Index][Next Report Section]

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National Institute on Drug Abuse

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

February, 2000

Research Findings

Services Research

Gender Differences in Drug Treatment Careers Among Clients in the National Drug Abuse Treatment Outcome Study

Gender differences were examined among 7,652 individuals admitted in the Drug Abuse Treatment Outcome Study, a national multi-site prospective study. Relationships between prior drug treatment, demographic and background characteristics, addiction career, treatment career parameters, family and social relationships, criminal justice involvement, and mental health status were examined. Stepwise discriminant function analyses were conducted separately for men and women to determine both the common and unique characteristics associated with a history of prior drug treatment. More severe drug use history and criminal behavior were related to prior treatment history for both men and women. Prior drug treatment among men was associated with factors related to family opposition to drug use and support for treatment, whereas for women prior drug treatment was associated with antisocial personality disorder and self-initiation into treatment. Treatment initiation among men appears to be facilitated by social institutions, such as employment, the criminal justice system, and one's family. Treatment re-entry among women was associated with referral by a social worker. These findings suggest that different strategies for increasing treatment utilization may be needed for men and women. Grella, C.E., and Joshi, V. American Journal of Drug and Alcohol Abuse, 25(3), pp. 385-406, August 1999.

Assessing the Needs of Substance Abusing Women. Psychometric Data on the Psychosocial History

The Psychosocial History (PSH) is a comprehensive multidisciplinary interview designed to assess the status, history, and needs of women in substance abuse treatment. The PSH retains the fundamental scoring structure of the Addiction Severity Index (ASI), while adding supplemental questions considered clinically useful and relevant for predicting outcomes. The present study examined the psychometric properties and general utility of both instruments with a sample of women enrolled in substance abuse treatment. Initially, the instruments were tested independently and found to have excellent test-retest reliability and acceptable internal consistency. A reliability trial between the instruments found that the composite scores (CS) of the ASI and PSH yielded satisfactory correlations among four of the six CS domains. The PSH had higher CS scores than the ASI across domains, which may reflect the comprehensive nature of the PSH items that prompt greater disclosure of problems and needs. Validity analyses showed significant correlations of PSH and ASI psychiatric CSs with Symptom Checklist-90-Revised totals. These results suggest that the PSH yields reliable and valid assessment data similar to the ASI. Moreover, the PSH provides a more comprehensive assessment than the ASI in the area of pregnancy, family issues, and victimization. Comfort, M., Zanis, D.A., Whiteley, M.J., Kelly-Tyler, A., and Kaltenbach K.A. Journal of Substance Abuse Treatment,17(1-2), pp. 79-83, 1999.

Psychiatric Comorbidity Measures as Predictors of Retention in Drug Abuse Treatment Programs

This study examined lifetime and current psychiatric comorbidity measures as predictors of drug abuse treatment retention and tested the generalizability of results across treatment agencies in diverse settings and with varying practices in the National Drug Abuse Treatment Outcome Studies (DATOS), a longitudinal study of clients from 96 treatment agencies in 11 U.S. cities. Clinical thresholds for adequate treatment retention were 90 days for long-term residential and outpatient drug-free, and 360 days for outpatient methadone. Dimensional measures of current psychiatric symptoms emerged as better predictors than lifetime DSM-III-R diagnoses. The predictive association of hostility with retention varied significantly across treatment agencies, both in long-term residential and outpatient drug-free modalities. On-site mental health services in long-term residential programs were associated with better retention for clients with symptoms of hostility. Broome, K.M., Flynn, P.M., and Simpson, D.D. Health Services Research, 34(3), pp. 791-806, August 1999.

Help-Seeking by African American Drug Users: A Prospective Analysis

In this study, help-seeking was significantly more likely for African American drug users with more formal education and those scoring higher on both drug-related problem recognition and ethnic identity. This latter result suggests that ethnic identity, despite having no main effect on help-seeking in this sample, may nonetheless make an important contribution to help-seeking by "potentiating" the influence of drug problem recognition. Longshore, D. Addictive Behaviors, 24(5), pp. 683-686, 1999.

Methadone Maintenance and State Medicaid Managed Care Programs

Coverage for methadone services in state Medicaid plans may facilitate access to the most effective therapy for heroin dependence. State Medicaid plans were reviewed to assess coverage for methadone services, methadone benefits in managed care, and limitations on methadone treatment. Medicaid does not cover methadone maintenance medication in 25 states (59 percent). Only 12 states (24 percent) include methadone services in Medicaid managed care plans. Moreover, two of the 12 states limit coverage for counseling or medication and others permit health plans to set limits. State authorities for Medicaid and substance abuse can collaborate to ensure that appropriate medication and treatment services are available for Medicaid recipients who are dependent on opioids and to construct payment mechanisms that minimize incentives that discourage enrollment among heroin-dependent individuals. McCarty, D., Frank, R.G., and Denmead, G.C. Milbank Quarterly, 77(3), pp. 341-362, 1999.

Modified Therapeutic Community for Homeless Mentally Ill Chemical Abusers: Emerging Subtypes

This paper is one of a series reporting on a clinical field trial evaluating the efficacy of the modified therapeutic community (TC) approach for the treatment of homeless mentally ill chemical abusers (MICAs). The social and psychological characteristics of the treatment sample were described in an earlier paper; the purpose of the present report was to categorize subtypes of homeless MICA clients to predict with greater accuracy their treatability in modified TCs. An index that consistently correlated with treatment-relevant variables was identified for each of three dimensions; Homelessness (residential instability), Mental Illness (current severity), and Substance Abuse (current substance abuse/dependence diagnosis). These indices yielded distributions that captured the variability in the sample with respect to a number of variables, including drug use, criminality, human immunodeficiency virus (HIV) risk (sexual behavior), psychological status, and motivation. Bivariate and multivariate analyses showed that the indices were not strongly related to demographic variables such as race/ethnicity, age, or gender, but were significantly associated with baseline drug use, criminal activity, HIV risk (sexual behavior), psychological symptoms, and motivation and readiness. These findings indicate that, even among those admitted to residential treatment for substance abuse, homeless MICA clients are not homogeneous; rather, subgroup differences emerge among the indices of homelessness, mental illness, and substance abuse. The efficacy of treatment in modified TCs for these subgroups will be assessed in subsequent papers examining the relationships among the three indices, client retention, and outcomes during and subsequent to residential treatment. De Leon, G., Sacks, S., Staines, G., and McKendrick K. Am J Drug Alc Abuse, 25(3), pp. 495-515, 1999.

The Relationship of Counseling and Self-Help Participation To Patient Outcomes in DATOS

Using a sample of 927 cocaine patients enrolled in programs in three modalities included in the national Drug Abuse Treatment Outcome Studies (DATOS), this investigation examined the relationship of three dimensions of treatment process on after-treatment cocaine use, heavy alcohol use, and predatory illegal activity. Logistic regression revealed significant reductions in all three outcomes and strong effects of treatment duration and after-treatment self-help, conditional on the modality. Results did not support the hypothesized relationship between treatment outcomes and amounts of counseling and during-treatment self-help. Findings support the robustness of duration effects and after-

treatment self-help and contribute to the measurement methodology for calibrating treatment intensity. The strong after-treatment self-help effect in the two residential and inpatient modalities suggests these programs can improve treatment outcomes by making referral to after-treatment self-help participation a standard practice and installing mechanisms to increase the likelihood of attendance at least twice weekly during the year after treatment. Etheridge, R.M., Craddock, S.G., Hubbard, R.L., and Rounds-Bryant, J.L. Drug and Alcohol Dependence, 57(2), pp. 99-112, 1999.

Retention and Patient Engagement Models for Different Treatment Modalities in DATOS

Using data from the Drug Abuse Treatment Outcomes Studies (DATOS), structural equation models tested the relationship between session attributes (e.g., relative frequency that addiction was discussed relative to health and other topics, number of sessions attended) and therapeutic involvement (e.g., rapport with counselor, confidence in treatment) during the first month of treatment as they related to patient retention in treatment for 90 or more days. Confirmatory results were replicated across different treatment approaches; outpatient drug free, long-term residential, and outpatient methadone maintenance. Session attributes were related to patient therapeutic involvement, and in turn to retention in treatment. In addition, session attributes and therapeutic involvement were demonstrated to be significant mediators of the relationship between pre-treatment motivation levels and treatment retention. Joe, G.W., Simpson, D.D., and Broome, K.M. Drug and Alcohol Dependence, 57, pp. 113-125, 1999.

Patient and Program Attributes Related to Treatment Process Indicators in DATOS

Using data from the Drug Abuse Treatment Outcomes Studies (DATOS), hierarchical linear modeling was used to examine the relationship between patient and drug abuse treatment program attributes and retention in treatment. Results showed that both patient and program attributes affected retention in treatment. High-patient retention programs were those that used more social and public health services, maintained more consistent attendance at counseling sessions, and that served patients who had more similar kinds of needs. High-treatment retention patients were those who possessed high levels of intrinsic motivation to participate in treatment, who expressed confidence that treatment will reduce their drug abuse, and expressing high levels of commitment to complete treatment. Broome, K.M., Simpson, D.D., and Joe, G.W. Drug and Alcohol Dependence, 57, pp. 127-135, 1999.

Prior Treatment Experience Related to Process and Outcomes in DATOS

Data collected as part of the Drug Abuse Treatment Outcomes Studies (DATOS) were used to examine the role of prior treatment history in affecting drug treatment outcomes among cocaine abusers. The focus of this study was to identify factors related to improved outcomes for the prior-treatment population. Patients with histories of prior treatment had less favorable post-treatment outcomes. Participation in aftercare self-help and living in an environment with few drug abusers was a significant factor in reducing drug abuse for patients with prior-treatment histories. Hser, Y-I, Grella, C.E., Hsieh, S-H., Anglin, M.D., and Brown, B.S. Drug and Alc Dep, 57, pp. 137-150, 1999.

Patient Histories, Retention, and Outcome Models for Younger and Older Adults in DATOS

Using data from the Drug Abuse Treatment Outcomes Studies (DATOS), structural equation models examined the role of age on treatment retention and post-treatment abstinence for outpatient drug free (ODF) and long-term residential (LTR) patients. Results showed a significant path between retention and abstinence, but retention had a greater impact on abstinence for younger patients. Regardless of age and treatment type, patient confidence in staying abstinent was related to post treatment abstinence. However, for LTR patients, social reference group (drug abusers/non-abusers) at follow-up had a significant relationship with patient confidence in staying abstinent and actual abstinence for young patients, but not older ones. For ODF patients social reference group at follow-up was shown to have a relatively greater impact on confidence in staying abstinent for older patients. Grella, C. E., Hser, Y-I., Vandana, J., and Anglin, M.D. Drug and Alcohol Dependence, 57, pp. 151-166, 1999.

Costs and Benefits of Treatment for Cocaine Addiction in DATOS

Data from the Drug Abuse Treatment Outcomes Studies (DATOS) were used to examine the economic benefits associated with treating cocaine addiction. Three methods were used to estimate the costs of crimes before, during, and after completing either outpatient drug free (ODF) or long-term residential (LTR) treatment. Results showed that cocaine treatment was economically beneficial to society. The savings due to reduced criminality far exceeded the cost of treatment. Treatment cost to criminal cost/benefit ratios ranged between 1.68 and 2.73 for LTR and between 1.33 and 3.26 for ODF patients depending on estimation methods used. Flynn, P.M., Kristiansen, P.L., Porto, J.V., and Hubbard, R.L. Drug and Alcohol Dependence, 57, pp. 167-174, 1999.

Feasibility of Multidimensional Substance Abuse Treatment Matching: Automating the ASAM Patient Placement Criteria

The Patient Placement Criteria published by the American Society of Addiction Medicine (ASAM Criteria) established a standard for matching substance use disorder patients to treatment settings. Data from 593 substance dependent adults were assessed using a computerized implementation of the ASAM Criteria to determine whether the level of care assignments showed significant differences on clinical measures. The algorithm showed acceptable discrimination between each of three ASAM levels of care across several clinical subscales. Findings suggest that it is feasible to implement complex, multidimensional criteria for substance abuse treatment placement. Turner, W.M., Turner, K.H., Reif, S., Gutowski, W.E., and Gastfriend, D.R. Drug and Alcohol Dependence, 55(1-2), pp 35-43, June 1, 1999.

Detection of Illicit Opioid and Cocaine Use in Methadone Maintenance Treatment

Urine toxicology is the gold standard for estimating the prevalence of illicit drug use in methadone maintenance treatment (MMT). Infrequent urine testing may lead programs to undercount active drug users and to target interventions too narrowly. This study compared results from frequent testing (twice per week) versus less frequent testing of 166 patients at four MMT programs. As part of a research study, all patients were tested by research staff for opioid and cocaine use twice per week on a fixed schedule for 10 weeks. During the same period, the four MMT programs tested the patients according to their standard protocols, approximately weekly (one program) or every 3-4 weeks (three programs). The research tests identified approximately 50% more illicit opioid users and 70% more cocaine users than the less frequent program tests. Patients who were drug positive according to the research tests but drug negative according to the program tests tended to be infrequent users. The data suggest that standard urine testing practices in MMT programs may result in underestimates of the prevalence of opioid and cocaine use. More frequent testing, even for time-limited periods, should produce more accurate depictions of drug use prevalence and help indicate the direction of interventions. Wasserman, D.A., Korcha, R., Havassy, B.E., and Hall S.M. Am J Drug Alc Abuse, 25(3), pp. 561-571, 1999.

Day Treatment Versus Enhanced Standard Methadone Services for Opioid-Dependent Patients: A Comparison of Clinical Efficacy and Cost

This study examined the differential efficacy and relative costs of two intensities of adjunctive psychosocial services -- a day treatment program and enhanced standard care -- for the treatment of opioid-dependent patients in methadone maintenance treatment. Both interventions were 12 weeks in duration, manual-guided, and provided by master's-level clinicians. The day treatment was an intensive, 25-hour-per-week program. The enhanced standard care was standard methadone maintenance plus a weekly skills training group and referral to on- and off-site services. Although the cost of the day treatment program was significantly higher, there was no significant difference in the two groups' use of either opiates or cocaine. Over the course of treatment, drug use, drug-related problems, and HIV risk behaviors decreased significantly for patients assigned to both treatment intensities. Improvements were maintained at a 6 month follow-up. Providing an intensive day treatment program to unemployed, inner-city methadone patients was not cost-effective relative to a program of enhanced methadone maintenance services, which produced comparable outcomes at less than half the cost. Avants, S.K., Margolin, A., Sindelar, J.L., Rounsaville, B.J., Schottenfeld, R., Stine, S., Cooney, N.L., Rosenheck, R.A., Li, S.H., and Kosten T.R. Am J Psychiatry, 156(1), pp. 27-33, January 1999.

[Office of the Director][Report Index][Next Report Section]

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National Institute on Drug Abuse

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

February, 2000

Research Findings

Intramural Research

Treatment Section, Clinical Pharmacology and Therapeutics Research Branch

Low-Dose Oral Cocaine in Humans: Acquisition of Discrimination and Time Course of Effects

As a tool for initial human screening of new anti-addictive compounds, oral cocaine may have practical advantages over intravenous, intranasal, or smoked cocaine. However, the nature and extent of its effects need further characterization. We tested the discriminability, subjective effects, and cardiovascular effects of 50 mg oral cocaine vs. placebo in seven cocaine-abusing volunteers across 50 two-hour sessions. Our behavioral-testing procedure permitted precise measurement of the time course of drug effects within sessions. Oral cocaine's effects began at a longer latency than has been reported for other routes, and had a longer duration. Six out of seven participants acquired the discrimination (though this typically required 15 to 30 sessions). In most participants, oral cocaine produced increases in ratings of "liking," "alertness," and "good effects," and in motor performance. Nonetheless, for most participants, peak heart rate and blood pressure remained within the range seen with placebo. Additional testing with one participant suggested that oral cocaine was discriminable and reinforcing at 25 mg and possibly 12.5 mg. The results support the discriminability of oral cocaine (and the sensitivity of the behavioral-testing procedure used). However, there were some intriguing dissociations between oral cocaine's discriminability and its identifiability. Epstein, D., Silverman, K., Henningfield, J.E., and Preston, K.L. Behavioural Pharmacology, 10, pp. 531-542, 1999.

Naltrexone Shortened Opioid Detoxification with Buprenorphine

In a double-blind, randomized clinical trial we evaluated the impact on withdrawal symptoms of combining naltrexone to a 4-day sublingual buprenorphine taper for short opioid detoxification. The experimental group (NB; n = 32) received placebo on day 1 and escalating doses of oral naltrexone on days 2-8; the control group (PB; n = 28) received placebo on days 1-7 and naltrexone on day 8. Main outcome measures were observer-rated withdrawal and use of medications for opioid withdrawal. Most (59%) patients in the NB group experienced clinically relevant withdrawal on day 2, but none after day 5. In contrast, withdrawal increased over time in the PB group. Withdrawal signs precipitated by the first naltrexone dose were similar in intensity whether on day 2 of the buprenorphine taper (NB) or on day 8 (4 days after the last buprenorphine dose; PB). However, 7 patients in the NB group dropped out on day 2, while only one patient dropped out in the PB group on day 8. Both groups received similar amounts of adjunct medication, with only 25% requiring sedatives. Initiating naltrexone on day 2 appears to abolish withdrawal symptoms after day 5, thus shortening the duration of withdrawal symptoms, and peak withdrawal was of moderate intensity. Thus, naltrexone combined with buprenorphine is an acceptable and safe procedure for shortened opioid detoxification and induction of naltrexone maintenance. Umbricht, A., Montoya, I.D., Hoover, D.R., Demuth, K.L., Chiang, C.-T., and Preston, K.L. Drug and Alcohol Dependence, 57, pp. 181-190, 1999.

Monitoring Cocaine Use in Substance Abuse Treatment Patients by Sweat and Urine Testing

Sweat and urine specimens were collected from methadone maintenance patients to evaluate sweat testing to monitor cocaine use. Paired sweat patches worn for one week; urine specimens collected three times weekly. All

patches (N = 930) were analyzed by ELISA immunoassay (cutoff concentration 10 ng/mL); a subset (N = 591) were also analyzed by GC-MS for cocaine, benzoylecgonine (BZE), and ecgonine methyl ester (EME) (cutoff concentration 5 ng/mL). Urine specimens were analyzed qualitatively (cutoff 300 ng/mL), and subsets were analyzed semiquantitatively (LOD = 30 ng/mL) and by GC-MS for cocaine (LOD = 5 ng/mL). Results were evaluated to determine the relative amounts of cocaine and its metabolites in sweat, assess replicability in duplicate patches, compare ELISA and GC-MS analyses in sweat, and compare the detection of cocaine in sweat and urine. Cocaine was detected by GC-MS in 99% of ELISA positive sweat patches; median concentrations of cocaine, BZE and EME were 378, 78.7 and 74 ng/mL. Agreement in duplicate patches was approximately 90% by ELISA analysis. Sensitivity, specificity and efficiency of sweat ELISA cocaine results as compared to sweat GC-MS results were all between 91 and 94%. Sensitivity, specificity and efficiency between ELISA sweat patch and qualitative urine results were 97.6%, 60.5%, and 77.7%. These results support the utility of sweat patches for monitoring cocaine use. Preston, K.L., Huestis, M.A., Wong, C.J., Umbricht, A., Goldberger, B.A., and Cone, E.J. Journal of Analytical Toxicology, 23, pp. 313-322, 1999.

Chemistry & Drug Metabolism Section, Clinical Pharmacology and Therapeutics Branch

Selective Deficits in Reflective Cognition of Polydrug Abusers

Reflective cognitive processing has been shown to be impaired in detoxified alcoholics who were otherwise cognitively intact. The goal of this study was to determine if substance abusers exhibited similar specific cognitive deficits. Fifteen subjects with histories of polydrug abuse and 15 normal control subjects were administered a series of cognitive tests. The tests assessed various learning and memory functions, including explicit and implicit memory, meta-cognition, working memory, memory consolidation, retrieval of information from long-term memory, and access to knowledge in long-term memory. Substance abusers did not differ from controls with respect to most cognitive domains, especially under conditions of stimulus-driven processing. However, substance abusers were impaired in using previously acquired knowledge and implicit memory on unstructured processing tests (fragmented pictures) and in inhibiting intrusion errors in word recall. These deficits in reflective functioning were negatively correlated with education and were most evident in subjects who did not graduate from high school. Deficits in reflective functioning are associated with drug-seeking and drug-taking behaviors and may be a risk factor for the initiation or maintenance of substance use disorders. Heishman, S.J., Weingartner, H.J., and Henningfield, J.E. Psychology of Addictive Behaviors, 13, pp. 227-231, 1999.

Medicinal Chemistry Section, Medications Discovery Research Branch

2D and 3D QSAR Modeling of Dopamine Transporter Ligands

We have synthesized >100 analogs of benztropine as novel probes for the dopamine transporter. Many of these compounds demonstrate high affinity and selectivity for the dopamine transporter and yet do not share a behavioral profile with cocaine in animal models of psychostimulant abuse. We have hypothesized that these compounds may be interacting at a binding domain on the dopamine transporter that is distinct from cocaine and that this may, in part, be related to their distinctive behavioral profile. This suggests that it may be possible to design dopamine uptake inhibitors that have therapeutic value for cocaine abuse treatment without inherent abuse potential. In order to study further the relationship of the structures of these compounds to their binding domain, we have begun to implement several molecular modeling techniques. Comparative Molecular Field Analysis (COMFA) derives the relationship between 3D-structures with binding affinities and provides a steric and electronic description of the binding domain of these ligands at the dopamine transporter. The contour maps that have been derived from the benztropines do indeed differ from those derived for cocaine and its analogs. Furthermore, these studies have confirmed structure-activity relationships previously derived in these series of compounds and now provide highly predictive models (q2=0.78) with which new ligands can be designed. In addition, a 2D QSAR model has been derived using Genetic Algorithm Partial Least Squares methodology. This highly predictive model (q2=0.88) has been used to screen the NCI database and a number of potential new leads with structural diversity have been discovered. It is anticipated that these studies will lead to the design of novel probes for the dopamine transporter and may provide clues toward a cocaine abuse therapeutic. Newman, A.H., Robarge, M., Izenwasser, S., and Kline, R.H. Journal of Medicinal Chemistry, 42, pp. 3502-3509, 1999.

Clinical Psychopharmacology Section, Medications Discovery Research Branch

GBR12909 Attenuates Amphetamine-induced Striatal Dopamine Release as Measured by [11C]raclopride

Continuous Infusion PET Scans

Major neurochemical effects of methamphetamine include release of dopamine (DA), serotonin (5-HT) and norepinephrine (NE) via a carrier-mediated exchange mechanism. Preclinical research supports the hypothesis that elevations of mesolimbic DA mediate the addictive and reinforcing effects of methamphetamine and amphetamine. The present study determined the ability of GBR12909 to attentuate amphetamine-induced increases in striatal DA as measured by [11C]raclopride continuous infusion PET scans in two Papio Anubis baboons. [11C]Raclopride was given in a continuous infusion paradigm. A 1.5 mg/kg amphetamine i.v. bolus was administered which caused a significant (30.3%) reduction in the volume of distribution (V3). The percent reduction in the volume of distribution and hence a measure of the intrasynaptic DA release ranged between 22 and 41%. GBR12909 (1 mg/kg, slow i.v. infusion) was administered 90 min before the administration of the radiotracer. GBR12909 inhibited amphetamine-induced dopamine release by 74%. Previous studies showed that 1 mg/kg GBR12909 occupies about 20% of DA transporters in the brain. The present results demonstrate that relatively low DA transporter occupancies by GBR12909 can substantially reduce amphetamine-induced DA release. These occupancy levels are achievable in humans administered GBR12909 via the oral route. Thus, these experiments suggest that GBR12909 is an important prototypical medication to test the hypothesis that stimulant-induced euphoria is mediated by DA, and, if the DA hypothesis is correct, a potential treatment agent for cocaine and methamphetamine abuse. Villemagne, V.L., Wong, D.F., Yokoi, F., Stephane, M., Rice, K.C., Matecka, D., Clough, D.J., Dannals, R.F., and Rothman, R.B. Synapse, 33, pp. 268-273, 1999.

Molecular Neuropsychiatry Section, Cellular Neurobiology Branch

Reversal by Delta Opioid Peptide, DADLE, of the Striatal Dopaminergic Damage Caused by Methamphetamine

Methamphetamine (METH) has been known to cause striatal dopaminergic (DA) damage. We have shown in the past that a pretreatment of delta opioid peptide DADLE can block the striatal DA damage caused by METH. Considering the potential clinical relevance of the use of DADLE, it would be of interest to examine if DADLE can "reverse" a pre-existing brain damage caused by METH. Two weeks after METH administration, a 75% loss of DA transporters was found in the striatum of CD-1 mice. An injection of DADLE, on day 14 after the METH treatment, was able to restore the DA transporter level back to the control. These results confirm the neuroprotective property of DADLE and suggest a potential use of DADLE in treating psychostimulant-induced brain damage. Tsao, L.-I., Cadet, J.L. and Su, T.-P. European Journal of Pharmacology, 372, pp. R5-R7, 1999.

Molecular Neuropsychiatry Section, Cellular Neurobiology Branch

Null Mutation of c-Fos Causes Exacerbation of Methamphetamine-induced Neurotoxicity

Methamphetamine neurotoxicity has been demonstrated in rodents and nonhuman primates. These neurotoxic effects may be associated with mechanisms involved in oxidative stress and the activation of immediate early genes (IEG). It is not clear, however, whether these IEG responses are involved in a methamphetamine-induced toxic cascade or in protective mechanisms against the deleterious effects of the drug. As a first step toward clarifying this issue further, the present study was thus undertaken to assess the toxic effects of methamphetamine in heterozygous and homozygous c-fos knockout as well as wild-type mice. Administration of methamphetamine caused significant reduction in [(125)I]RTI-121-labeled dopamine uptake sites, dopamine transporter protein, and tyrosine hydroxylase-like immunohistochemistry in the striata of wild-type mice. These decreases were significantly exacerbated in heterozygous and homozygous c-fos knockout mice, with the homozygous showing greater loss of striatal dopaminergic markers. Moreover, in comparison with wild-type animals, both genotypes of c-fos knockout mice showed more DNA fragmentation, measured by the number of terminal deoxynucleotidyl transferase-mediated dUTP nick-end-labeled nondopaminergic cells in their cortices and striata. In contrast, wild- type mice treated with methamphetamine demonstrated a greater number of glial fibrillary acidic protein-positive cells than did c-fos knockout mice. These data suggest that c-fos induction in response to toxic doses of methamphetamine might be involved in protective mechanisms against this drug-induced neurotoxicity. Deng X., Ladenheim B., Tsao L., and Cadet J.L., Journal of Neuroscience, 19, pp. 10107-10115, 1999.

Dual Mechanism of Fas-induced Cell Death in Neuroglioma Cells: a Role for Reactive Oxygen Species

ApoI/Fas belongs to the tumor necrosis factor receptor (TNFR) superfamily and mediates cell death in various cell types. A dual mode of Fas-triggered cell death has been reported depending on cell types used in the experiments. The present study was carried out to test the possible role of reactive oxygen species in this dual mechanism in

neuroglioma cells. Anti-Fas antibody caused dose-dependent and time- dependent increases in cell death measured by lactate dehydrogenase (LDH) release in control neuroglioma cells and in cells that were transfected with catalase cDNA. However, cells transfected with copper/zinc superoxide dismutase (Cu/ZnSOD) cDNA showed marked attenuation of Fas-induced LDH release. Moreover, flow cytometry and confocal microscopy revealed that Fas-induced cell death in control cells occur mostly through an apoptotic process. This process was also completely abrogated in cells overexpressing catalase or copper/zinc superoxide dismutase (Cu/ZnSOD). Further experiments revealed that Fas-induced cell death was associated with increased formation of Superoxide anions in control neuroglioma cells and in cells overexpressing catalase. Increases were significantly suppressed by Cu/ZnSOD overexpression. These data indicate that Fas-mediated cell death in neuroglioma cells occur, in part, through the production of reactive oxygen species (ROS). These observations also suggest that Fas-induced cell death in these cells occur through apoptosis and necrosis. Thus overexpression of Cu/ZnSOD caused the suppression of both types of Fas-induced cell death whereas catalase prevented apoptotic but not necrotic cell death. These observations are discussed in terms of their support for a role for both peroxides and superoxide radicals in Fas- induced cell death. Jayanthi, S., Ordonez, S., McCoy, M.T., and Cadet, J.L. Molecular Brain Research, 72, pp. 158-165, 1999.

Differential Gene Expression in Methamphetamine Neurotoxicity Identified Using cDNA Arrays

Methamphetamine (METH) can cause damage to monoaminergic systems in mammals. A role for oxygen-based radicals in the neurotoxic effects of the drug is well supported by the accumulated literature. Thus far, however, very little is know about the contribution of various genes to the neurotoxic effects of METH. Using cDNA microarray technology, we have monitored the expression pattern of 196 stress- and apoptotic-related genes. MRNA for microarray hybridization was obtained from different brain regions of mice treated with a neurotoxic dose of METH and compared to saline-treated controls. The results show differential cortical expression of glutathione S-transferase; MmRad51; FAF1; Adenosine A1M receptor; T-lymphocyte activation gene; Vav; GDP-GTP exchange factor; Golgi-4-transmembrane spanning transporter and IRF1. Experiments are underway using other brain regions. This approach will be valuable for identifying genes that contribute to the neurotoxicity of METH and of other agents that cause neurodegenerative disorders. Jayanthi, S., Krasnova, I., Ladenheim, B., and Cadet, J.L., Poster, 1999. Society for Neuroscience Annual Meeting, Miami, FL, October 23-29, 1999.

Toxic Effects of Methamphetamine and Dopamine in Cell Culture

Methamphetamine (METH) and dopamine (DA) can cause neurotoxic damage both in vitro and *in vivo*. The mechanisms of action involve the increased production of free radicals. The present study was undertaken to compare and contrast the toxic effects of METH and DA by using an immortalized neural cell line. Both METH and DA caused dose-dependent increase in production of reactive oxygen species (ROS) and cell death. Cell death caused by these agents was characterized by cytoplasmic vacuolar formation, shrinkage of cytoplasm and nuclear dissolution. Flow cytometric evaluation also revealed that these toxins cause changes similar to those observed in cells undergoing apoptosis. Furthermore, DNA electrophoresis showed that both METH and DA induced DNA ladder formation. When taken together these observations suggest that METH and DA cause these cells to die via apoptosis. Further experiments indicated that growth of these cells in low (1%) serum or in the absence of serum markedly enhanced the apoptotic effects of both drugs. These data provide further support for the idea that both METH and DA can cause ROS-mediated apoptosis. Cadet, J.L., Ordonez, S. and Burrell, S., Poster, 1999. Oxygen Society Meeting, New Orleans, LA, November 17-22, 1999.

Neuroimaging Research Branch

[Br-76]BAP is a Novel Ligand for Imaging nAChRs

5-[Br-76]Bromo-3-[[2(S)-azetidinyl] methoxy]pyridine ([Br-76]BAP), a novel nicotinic acetylcholine receptor ligand, was synthesized using [Br-76]bromide and evaluated as a potential radiotracer for use with positron emission tomography (PET). The radiochemical yield was 25%, and the specific radioactivity was on the order of 1 Ci/micromol. In vitro studies using rat cortical and thalamic membranes demonstrated >90% of maximal specific [Br-76]BAP binding after 60 min. For cortical and thalamic membranes, the binding affinities (Kd) were 36 +/- 9 and 30 +/- 9 pM respectively. Although data were best fit by a single population of binding sites, Scatchard plots were nonlinear, and the Hill coefficients were <1, suggesting the presence of a lower-affinity binding site. Maximal binding site density (Bmax) values were 90 +/- 17 and 207 +/- 33 fmol/mg in the cortex and thalamus, respectively. In vitro and ex vivo autoradiography showed binding of [Br-76]BAP was high in the thalamus and presubiculum, moderate in the cortex and striatum, and low in the cerebellum and hippocampus. *in vivo* binding of [Br-76]BAP in whole rat brain was blocked by the preinjection of (S)(-)-nicotine (0.3 mg/kg) by 91% at 300 min. In PET studies using Rhesus monkeys, radiotracer accumulation was highest in the thalamus, and cytisine and nicotine effectively displaced thalamic radioactivity by 60% and by 50%, respectively. These results indicate that [Br-76]BAP is a promising

radioligand for characterizing nicotinic acetylcholine receptors *in vivo* using PET. Sihver, W., Fasth, K.J., Horti, A.G., Koren, A.O., Bergstrom, M., Lu, L., Hagberg, G., Lundqvist, H., Dannals, R.F., London, E.D., Nordberg, A., and Langstrom, B. J. Neurochem. 73(3), pp. 1264-72, 1999.

2-[18F]F-A-83580: A PET Radioligand for alpha4beta2 _Nicotinic Acetylcholine Receptors

Until recently noninvasive *in vivo* studies of central nicotinic acetylcholine receptors (nAChRs) have been impeded by the absence of appropriate radiotracers. Taking into account that central nAChRs have been implicated in a variety of brain functions, including cognitive processes, and also are affected in various pathological conditions, such as Alzheimer's and Parkinson's diseases, noninvasive imaging techniques such as PET, could be powerful tools for studying these receptors *in vivo*. A new compound for the alpha4beta2 subtype of nAChRs, 2-fluoro-A-85380, synthesized and labeled with F-18 by the NIDA radiochemistry group, has been evaluated in in vitro binding assays with membranes of rat brain and *in vivo* by PET in Rhesus monkey. The ligand has high affinity for alpha4beta2 nAChRs (Kd = 50 n), crosses the blood-brain barrier and distributes in brain regions known to contain high densities of alpha4beta2 nAChRs. A high level of specific binding was achieved 4 h after administration, as indicated by the thalamus-cerebellum/cerebellum radioactivity ratio of 3.3. The specificity of binding was confirmed by displacement study with cytisine. These results, in combination with data demonstrating low toxicity of 2-[F-18]F-A-85380, indicate that this radiotracer is an excellent candidate for PET imaging of central nAChRs in human subjects. Chefer, S.I., Horti, A.G., Koren, A.O., Gundisch, D., Links, J.M., Kurian, V., Dannals, R.F., Mukhin, A.G., and London, E.D. NeuroReport, 10, pp. 2715-2721, 1999.

Comparison Study of [C-11]iomazenil and [I-123]iomazenil by PET and SPECT

Although PET and single photon emission computed tomography (SPECT) are increasingly used for quantitation of neuroreceptor binding, almost no studies to date have involved a direct comparison of the two imaging techniques. One study found a high level of agreement between the two techniques, although there was a systematic 30% increase in measures of benzodiazepine receptor binding in SPECT compared with PET. The purpose of the current study was to directly compare quantitation of benzodiazepine receptor binding in the same human subjects using PET and SPECT with high specific activity [C-11]iomazenil and [I-123]iomazenil, respectively. All subjects were administered a single bolus of high specific activity iomazenil labeled with C-11 or I-123 followed by dynamic PET or SPECT imaging of the brain. Arterial blood samples were obtained for measurement of metabolite-corrected radioligand in plasma. Compartmental modeling was used to fit values for kinetic rate constants of transfer of radioligand between plasma and brain compartments. These values were used to calculate binding potential (BP=Bmax/Kd) and the fraction of free non-protein-bound parent compound (V3'). Mean values for V3' in PET and SPECT were as follows: temporal cortex 23±5 and 22±3 ml/g, frontal cortex 23±6 and 22±3 ml/g, occipital cortex 28±3 and 31±5 ml/g, and striatum 4±4 and 7±4 ml/g. These preliminary findings indicate that PET and SPECT provide comparable results in quantitation of neuroreceptor binding in the human brain. Bremner, J.D., Baldwin, R., Horti, A., Staib, L.H., Ng, C.K., Tan, P.Z., Zea-Ponce, Y., Zoghbi, S., Seibyl, J.P., Soufer, R., Charney, D.S., and Innis, R.B. Psychiatry Res.: Neuroimaging, 91, pp. 79-91, 1999.

Methylphenidate and Neuroimaging

In June 1995 a research article appeared in the Archives of General Psychiatry (Volkow et al. 1995) and asked the provocative question "Is methylphenidate like cocaine?". This question was addressed by examining the cerebral location and time course of the effects of these drugs using functional neuroimaging. The answer is not simple. Although these drugs have similar mechanisms of action, there are more subtle differences that make methylphenidate a safe and effective medication for the treatment of attention-deficit hyperactivity disorder, and cocaine an addictive and dangerous agent. To assist in the interpretation of brain imaging literature, this review addresses briefly the pharmacology of cocaine and methylphenidate, the basic principles of brain imaging techniques, and the strategies used to map and quantify the effects of pharmacological agents in the living human brain. Ernst, M., Earle, A., and Zametkin, A.J. In: Ritalin: Theory and Practice, Laurence L. Greenhill and Betty Osman, eds, Mary Ann Liebert, Inc. Publishers, pp. 375-384, 1999.

[Office of the Director][Report Index][Next Report Section]

Archive Home | Accessibility | Privacy | FOIA (NIH) | Current NIDA Home Page

National Institute on Drug Abuse

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

February, 2000

Program Activities

New PAs/RFAs

A newly revised Program Announcement entitled **"Research on the Origins and Pathways to Drug Abuse", (PAR-99-168,** September 30, 1999) replaces PA-97-043, which was published in the NIH Guide, Vol. 26, No. 8, March 14, 1997. This PA encourages research exploring the origins of and pathways to drug abuse and addiction. Of particular interest are multidisciplinary, integrative, and developmental approaches. A complete copy of the PA including more information about the research that the PA seeks to encourage can be found at: http://grants.nih.gov/grants/guide/pa-files/PAR-99-168.html.

A Program Announcement entitled **"Drug Abuse Prevention Intervention Research" (PA-00-002)** was issued in the NIH Guide on October 5, 1999. This PA encourages research to examine the efficacy and effectiveness of new and innovative theory-based prevention approaches; to determine the components of research-based intervention strategies and programs that account for effectiveness of approaches; to clarify factors related to the effective and efficient provision of prevention services; and to develop and test methodologies appropriate for studying these complex aspects of prevention science.

On November 2, 1999, NIDA issued a Program Announcement entitled **"Social Work Research Development Program" (PAR-00-008)** announcing the availability of support for a Social Work Research Development Program (SWRD) focused on the development of social work research in all areas of drug abuse intervention and services research. The goals of this program are to build a stable infrastructure for drug abuse research in schools of social work and to increase interdisciplinary participation in drug abuse research in order to improve the quality of interventions aimed at reducing drug abuse and addiction in this country.

On January 19, 2000, NIDA issued a Program Announcement entitled **"Neurobiological and Behavioral Research on Nicotine and Tobacco Components" (PA-00-045).** The purpose of this PA is to encourage research on any aspect of the effects of nicotine and other tobacco components, using neurobiological, behavioral, or other methods in humans, animals, or in vitro systems, that seeks to explain nicotine use, addiction, or other effects in humans.

On October 8, 1999, NIDA, in conjunction with numerous other NIH Institutes, issued a PA entitled **"Mentored Clinical Scientist Development Award (K08)" (PA-00-003).** The purpose of this PA is to support the development of outstanding clinician research scientists. This mechanism provides specialized study for individuals with a health professional doctoral degree committed to a career in laboratory or field-based research.

On October 8, 1999, NIDA, in conjunction with numerous other NIH Institutes issued a PA entitled **"Mentored Patient-Oriented Research Career Development Award (K23)" (PA-00-004).** The purpose of this PA is to support the career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research.

On October 8, 1999, NIDA, in conjunction with numerous other NIH Institutes issued a PA entitled **"Midcareer Investigator Award in Patient-Oriented Research (K24)" (PA-00-005).** The purpose of this PA is to provide support for clinicians to allow them protected time to devote to patient-oriented research and to act as mentors for

beginning clinical investigators.

On November 30, 1999, NIDA, in conjunction with numerous other NIH components, issued a revision of the PA entitled **"Bioengineering Research Partnerships" (PAS-00-006).** This PA invites applications for R01 awards to support Bioengineering Research Partnerships (BRPs) for basic bioengineering research addressing important biological or medical research problems. A BRP is a multidisciplinary research team applying an integrative, systems approach to develop knowledge and/or methods to prevent, detect, diagnose and treat disease and understand health and behavior. The partnership must include bioengineering expertise in combination with basic and/or clinical investigators. A BRP may propose design-directed or hypotheses-driven research in universities, national laboratories, medical schools, private industry and other public and private entities.

On December 2, 1999, NIDA, in conjunction with numerous other NIH components issued a PA entitled **"Bioengineering Nanotechnology Initiative" (PA-00-018).** This PA, issued as an initiative of the trans-NIH Bioengineering Consortium (BECON), invites applications for Small Business Innovation Research (SBIR) projects on nanotechnologies useful to biomedicine. Nanotechnology, the creation of functional materials, devices and systems through control of matter at the scale of 1 to 100 nanometers, and the exploitation of novel properties and phenomena at the same scale is emerging as a field critical for enabling essential breakthroughs that may have tremendous potential for affecting biomedicine.

On December 2, 1999, NIDA, in conjunction with numerous other NIH Institutes issued a PA entitled **"Mentored Research Scientist Development Award (K01)" (PA-00-019).** This award provides for an intensive, supervised career development experience in one of the biomedical, behavioral or clinical sciences leading to research independence.

On December 2, 1999, NIDA, in conjunction with numerous other NIH Institutes issued a PA entitled **"Independent Scientist Award (K02)" (PA-00-020).** This award provides up to five years of salary support for newly independent scientists who can demonstrate the need for a period of intensive research focus as a means of enhancing their research careers. This award is intended to foster the development of outstanding scientists and enable them to expand their potential to make significant contributions to their field of research.

On December 2, 1999, NIDA, in conjunction with NIAAA, NIMH, NCI and the National Center for Complementary and Alternative Medicine issued a PA entitled **"Senior Scientist Award K05)" (PA-00-021).** This award provides stability of support to outstanding scientists who have demonstrated a sustained, high level of productivity and whose expertise, research accomplishments, and contributions to the field have been and will continue to be critical to the mission of the particular NIH Center or Institute.

NIDA, in conjunction with a number of other NIH components issued a PA entitled **"The Role of Microglia in Normal and Abnormal Immune Responses of the Nervous System" (PA-00-029)** on December 15, 1999. This PA invites applications to promote research into the role of microglia in the initiation and expansion of autoimmune processes of the central nervous system (CNS) and the resulting injury to CNS components.

An RFA entitled **"Cognitive Approaches to Addictive Processes" (DA-01-001),** developed by the Cognitive Science Working Group (Chairs: Herbert Weingartner, Ph.D. and Steven Grant, Ph.D.) was released on November 22, 1999. This RFA invites applications in the area of cognitive science and cognitive neuroscience that have the potential of addressing issues related to drug abuse and addiction. The objective is to stimulate cognitive science and cognitive neuroscience research that has the potential to advance our understanding of the causes, consequences, neuronal basis and treatment of drug abuse and addictive processes. Cognitive research is encouraged that is model-driven; and either (1) explores and delineates basic cognitive processes related to drug abuse and addiction and vulnerability to drug addiction, or (2) directly studies drug abuse and the effects of drugs on particular aspects of cognitive functions. The Letter of Intent Receipt date is May 15, 2000, and the Application Receipt date is July 14, 2000.

On December 16, 1999, NIDA issued an RFA entitled **"Microarray-Based Research on Drug Abuse" (DA-00-003).** This RFA encourages innovative studies that exploit emerging microarray technology, adapting and applying these techniques to the general problem of drug abuse. The creation of collaborative teams that will develop innovative approaches for analyzing microarray data is encouraged. Letter of Intent Receipt date for this RFA is February 28, 2000; Application Receipt date is March 28, 2000.

On December 16, 1999, NIDA issued an RFA entitled **"Basic Behavioral, Cognitive, and Neurological Research: Applications to HIV/AIDS and Drug Abuse" (DA-00-005).** This RFA encourages applications for research projects in the basic behavioral, cognitive and neurosciences that can address the complex relationship between drug abuse and addiction and HIV/AIDS transmission and progression. Letter of Intent Receipt date for this RFA is February 29, 2000; Application Receipt date is March 29, 2000.

On December 20, 1999, NIDA reissued the RFA entitled **"National Drug Abuse Treatment Clinical Trials Network" (DA-00-002),** inviting applications from established clinical investigators to participate in the National Drug Abuse Treatment Clinical Trials Network (CTN). CTN research is carried out in community-based treatment settings, in collaboration with other awardees and with NIDA. This RFA is a second issue with the intention to develop a geographically diverse and encompassing network. The Letter of Intent Receipt date for this RFA is February 17, 2000; Application Receipt date is March 16, 2000.

On December 20, 1999, NIDA issued an RFA entitled **"HIV Therapy for Drug Users: Access, Adherence, Effectiveness" (DA-00-007).** The purpose of this RFA is to encourage applications for research on access, adherence and effectiveness relevant to the treatment of drug users with HIV. This initiative will support research on a broad range of HIV care-related issues. Letter of Intent Receipt Date for this RFA is February 28, 2000; Application Receipt Date is March 29, 2000.

On December 20, 1999, NIDA issued an RFA entitled **"The Next Generation of Drug Abuse Prevention Research" (DA-00-004)** which encourages applications to examine components of empirically validated drug abuse prevention interventions that may account for program effectiveness. The purpose is to gain a better understanding of what accounts for program effectiveness through: empirical tests of theoretically derived processes that may account for program effectiveness; identification of patterns related to differential effectiveness; generating and testing alternate hypotheses accounting for effectiveness based on differential outcomes from previous research; and specification and testing of components singularly and in combination that contribute to effectiveness. Letter of Intent Receipt Date for this RFA is February 28, 2000; Application Receipt Date is March 28, 2000.

On January 11, 2000, NIDA, in collaboration with NIAAA issued an RFA entitled **"Viral Hepatitis and HIV in Drug and Alcohol Users" (DA-00-006).** This RFA is intended to address gaps in prevention, natural history, pathogenesis and treatment research related to viral hepatitis infection in drug and/or alcohol users, both with and without concomitant HIV infection, with an emphasis on research related to co-infections. Letter of Intent Receipt Date for this RFA is February 28, 2000; Application Receipt Date is March 28, 2000.

On January 21, 2000, NIDA issued an RFA entitled **"Centers for Drug Abuse and AIDS Research Core Grants" (DA-00-008).** The purpose of the CDAAR Core Grants is to create centers to enhance basic, clinical, epidemiological, prevention,and applied research on drug abuse and HIV infection and other co-occurring illnesses, through the support of shared resources. Letter of Intent Receipt Date for this RFA is March 13, 2000; Application Receipt Date is April, 12, 2000.

On September 7, 1999, NIDA, in conjunction with numerous other NIH components, issued an RFA entitled **"Building Interdisciplinary Research Careers in Women's Health" (OD-99-008).** This RFA invites career development award applications from junior faculty members, to be known as Interdisciplinary Women's Health Research (IWHR) Scholars, who have recently completed clinical training or postdoctoral fellowships, and who are commencing basic, translational, clinical and/or health services research relevant to women's health.

NIDA, in conjunction with several other NIH Institutes, issued an RFA on November 22, 1999 entitled **"Gene Expression Profiling in the Nervous System" (MH-00-002).** The purpose of this RFA is to solicit feasibility studies for profiling gene expression patterns in the mammalian nervous system. Exploratory research projects supported under this RFA will utilize neural tissue-specific cDNA reagents and state of the art microarray technologies in order to quantify in a highly parallel way, expression profiles of genes in mammalian neural tissue. The creation of collaborative teams is encouraged in which scientists with expertise in neuroscience research, genomics, and bioinformatics work to apply innovative approaches for analyzing microarray data.

NIDA, along with numerous other NIH components is co-sponsoring a new trans-institute NIH RFA entitled **"Testing Interventions to Improve Adherence to Pharmacological Treatment Regimens" (OD-00-006).** The NIH Office of Behavioral and Social Sciences Research (OBSSR) coordinated the effort for this RFA, issued in the NIH Guide on January 19, 2000. The purpose of this RFA is to encourage behavioral and social research on the effectiveness of interventions to improve adherence to therapeutic regimens in various settings. Letter of Intent Receipt Date is March 6, 2000; Application Receipt Date is April 6, 2000.

Notices

On December 8, 1999 NIDA issued a Notice in the NIH Guide entitled **"Club Drug Research and Education Initiative" (DA-00-002).** The purpose of this Notice is to inform the research community that NIDA is interested in expanding its research portfolio on all aspects related to the use, abuse, short- and long-term effects of "club drugs".

On December 13, 1999 NIDA issued a Notice in the NIH Guide announcing the availability of **"Administrative**

Supplements for the Study of Drug Abuse and HIV/AIDS" (DA-00-003). The primary intent of this program is to encourage federal grantees who have not focused on drug use-related HIV/AIDS issues to do so, thus recognizing that drug abuse and HIV/AIDS are two diseases that often co-occur and interact and that must be prevented and treated together and in parallel. Projects that currently focus solely on either AIDS-related or drug abuse issues are encouraged to strengthen efforts in the complementary area.

Other Program Activities

National Drug Abuse Treatment Clinical Trials Network Grants Awarded

In an effort to dramatically improve treatment throughout the country, NIDA has awarded $55 million in grants over five years to establish a clinical trials network that will more rapidly move promising science-based drug addiction treatments into community settings. The five centers awarded grants are collectively the foundation for the National Drug Abuse Clinical Trials Network (CTN), which will provide a research infrastructure to test drug addiction treatments in real-life settings with diverse patient populations. The CTN will foster partnerships among NIDA, treatment researchers, and community-based treatment programs to bridge the gap between research and practice. The CTN, announced in January 1999 with an RFA, when complete, will consist of 20 to 30 regional research centers. At the local level, each center will be linked with 10 to 15 community treatment programs that represent a variety of treatment settings and patient populations available in that particular region of the country. The following universities have been selected as the cores for the first five regional centers. Each core will be linked with at least five community treatment programs throughout the region.

New England Node:	**Yale University, New Haven, CT**
Delaware Valley Node:	**University of Pennsylvania, Philadelphia, PA**
Mid-Atlantic Node:	**Johns Hopkins University, Baltimore, MD** **Medical College of Virginia, Richmond, VA**
Pacific Node:	**University of California at Los Angeles, Los Angeles, CA**
Northwest Node:	**Oregon Health Sciences University, Portland, OR**

Transdisciplinary Tobacco Use Research Centers

Seven academic institutions have been awarded grants totaling $14.5 million by the National Cancer Institute (NCI) and the National Institute on Drug Abuse (NIDA) to create the Transdisciplinary Tobacco Use Research Centers for studying new ways to combat tobacco use and its consequences. The Robert Wood Johnson Foundation (RWJF) has committed an additional $14 million over five years to complement NCI's and NIDA's efforts to improve the policy understanding and communications practices of the tobacco research teams. Each center, funded for five years, will foster unique collaborations among scientists across many disciplines, and will focus on areas where there are gaps in knowledge, such as adolescent smoking. Together, NCI and NIDA will spend about $70 million for the effort over five years. The centers' locations, principal investigators, and research themes follow.

The Brown University Center for Behavioral and Preventive Medicine at the Miriam Hospital, Providence, RI -- PI: David B. Abrams, Ph.D.
Theme: identify early childhood and lifetime psychiatric factors that determine smoking initiation, dependence, use patterns, cessation, and response to cessation treatment

The University of California at Irvine -- PI: Frances M. Leslie, Ph.D.
Theme: identify predictors of nicotine addiction in animals and tobacco susceptibility and use in humans using a shared conceptual model across multiple levels of analysis

The University of Southern California, Los Angeles -- PI: C. Anderson Johnson, Ph.D.
Theme: preventing tobacco use among youth of diverse cultures

Georgetown University, Washington, DC -- PI: Caryn Lerman, Ph.D.
Theme: identifying the bio-behavioral basis of smoking initiation, smoking treatment, and harm from tobacco exposure

University of Minnesota, Minneapolis -- PI: Dorothy K. Hatsukami, Ph.D.
Theme: treating smokers who have been resistant to conventional methods of intervention or who have not been previously targeted

University of Wisconsin Medical School, Madison -- PI: Michael Fiore, M.D., M.P.H.
Theme: relapse to tobacco use

Yale University, New Haven, CT -- PI: Stephanie S. O'Malley, Ph.D.
Theme: treatment of tobacco addiction

Buprenorphine/Naloxone New Drug Application

The New Drug Application for buprenorphine/naloxone, filed by Reckitt and Colman Pharmaceuticals, received an approvable status from the FDA on December 7, 1999. Both the buprenorphine and buprenorphine/naloxone New Drug Applications could be approved by mid-year 2000.

P-50 Center Grant Awards in Medications Development

DTR&D awarded a second group of P-50 center grants to the following persons and institutions: Dr. Herbert Kleber -- Columbia, University, NY; Dr. Marian Fishman -- Columbia University, NY; Dr. Tom Kosten -- Yale University, CT; Dr. Joseph Volpicelli -- University of Pennsylvania; and Dr. John Grabowski -- University of Texas, Houston.

Outpatient Study of Selegiline IR in Cocaine Dependence

A 4 site study of selegiline in the Department of Veterans Affairs Cooperative Studies Program (VACSP 1017) directed by Dr. Deborah Leiderman (DTR&D) has reached 60% enrollment. The trial should be completed by April 2000. A protocol for the Selegiline Transdermal System (STS) is currently undergoing review within the DVA and is projected to commence in the spring of 2000.

Drug Dependence and Neuroviral Infections

DTR&D has awarded a supplement to an NIMH grant to Dr. Ian Lipkin (as an Interagency agreement) to evaluate the concept that Antisocial Personality Disorder, which represents a major risk factor for development of refractory drug dependence, is associated with certain neuroviral infections. Based on preclinical data, it is hypothesized that such infections could alter brain biochemistry and make the infected individuals more vulnerable to drug dependence.

ONDCP National Youth Anti-Drug Media Campaign Evaluation

NIDA completed preparations for the evaluation of the ONDCP National Youth Anti-Drug Media Campaign and entered the field in November 1999. The complex science-based evaluation project is being conducted under contract with Westat, Inc., with two subcontractors, the Annenberg School for Communication, University of Pennsylvania, and the National Development Research Institute in North Carolina. The study, which is based on behavior change and social influence models, will be conducted in the household with parents and children in the same family. NIDA and the evaluation team spent approximately a year developing the research design, the six questionnaires for parents and youth, the sampling and analysis plans, programming of the questionnaires for laptop computers, and other extensive survey procedures. The study is being conducted at the national level with representative samples of parents and youth in a cross-sectional design and at the community level in four sites within major media markets in a longitudinal design. Reporting will take place every six months starting this summer with the report of the first wave.

Response to Child Neglect Research RFA

Seventy-three applications were submitted in response to RFA **Child Neglect Research (OD-99-006)** issued by the NIH Consortium on Child Abuse and Neglect for May 2000 Council. NIDA is the primary applicant institute on 8 of the applications and dual on 63. The NIDA contact is Dr. Coryl Jones (ERB/DESPR).

NIDA's New and Competing Awards Since September 1999

Abrams, David B. --- Miriam Hospital

Nicotine Dependence: Risk & Recovery Over Generations

Akil, Huda --- University of Michigan
The Orphanin System: Role In Stress and Addiction

Awbrey, James L. --- University of Georgia
Restructuring, Destructuring and Anonymous Organizations

Babich, John W. --- Zebra Pharmaceuticals, Inc.
Studies Of Novel Cocaine Medications Using PET

Barr, Gordon A. --- Hunter College of CUNY
MIDARP At Hunter College

Beinfeld, Margery C. --- Tufts University
Acute and Chronic Cocaine-Induced CCK Release

Bellack, Alan S. --- University of Maryland
Treatment For Substance Abuse In Schizophrenia

Bennett, Charles L. --- Northwestern University
Multicity Study of Quality of Care For HIV-Related TB

Benveniste, Helene D. --- Duke University
A 3D C57bl6/J Mouse Brain Atlas Magnetic Resonance Micro

Berkovitz, Robert A. --- Sensimetrics
Differential Spectrogram for Analysis of Nonlinearity

Berns, Gregory S. --- Emory University School of Medicine
Neuroimaging of Novelty Detection In Cocaine Dependence

Blendy, Julie A. --- University of Pennsylvania
Genetic Analysis of Drug Addiction

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

Boot, Lee R. --- Infoculture
Neuroscience TV to Steer Teens from Substance Abuse

Broadhead, Robert S. --- University of Connecticut
Increasing Drug Users' Adherence To HIV Therapeutics

Brook, Judith S. --- Mount Sinai School of Medicine
Childhood Etiologic Determinants of Adolescent Drug Use

Brooner, Robert K. --- Johns Hopkins Bayview Campus
Clinical Trials Network Mid-Atlantic Collaborative Group

Brown, C. H. --- University of South Florida
Designs and Analyses for Mental Health Preventive Trials

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

Burks, Thomas F. --- University of Texas Health Sciences Center
Opioid Gastrointestinal Tolerance and Dependence

Carey, Robert J. --- VA Medical Center
Interoceptive Drug Cue Conditioning of Cocaine Effects

Carise, Deni --- Treatment Research Institute
Linking Assessment Technology to Improved Patient Care

Carroll, Frank I. --- Research Triangle Institute

Selective Opioid Antagonist as Medication for Drug Abuse

Carroll, Kathleen M. --- Yale University
Clinical Trials Network: New England Node

Caton, Carol L. --- Columbia University
Drug Use and Course of Homelessness Among Single Adults

Chang, Linda --- Harbor-UCLA Research Education Institute
MR Spectroscopy to Monitor HAART In HIV Brain Injury

Chassin, Laurie A. --- Arizona State University
Substance Use Among Children of Alcoholics

Chavkin, Charles --- University of Washington
Endogenous Opioid Peptide Action In the Hippocampus

Chenausky, Karen V. --- Speech Technology & Applied Research Corp.
Automatic Analysis and Diagnosis of Dysarthria

Cheney, Paul D. --- University of Kansas Medical Center
Neuro-AIDS In Opiate Dependent Rhesus Macaques

Chiauzzi, Emil J. --- Innovative Training Systems
An Alternative for Incarcerated Substance Abusers

Childers, Steven R. --- Wake Forest University School of Medicine
Endogenous Cannabinoid Systems In Brain

Chiriboga, Claudia A. --- Neurological Institute
Quantified Fetal Cocaine Exposure and Neurodevelopment

Clark, Ann S. --- Dartmouth College
Neural and Behavioral Actions of Anabolic Steroids

Collins, Rebecca L. --- RAND
Substance Use and Sexual Risk Among HIV Positive Adults

Cottler, Linda B. --- Washington University
Prevention of HIV & STDs In Drug Using Women

Criado, Jose R. --- Scripps Research Institute
Cognitive and Reward Mechanisms In Opiate Addiction

Daunais, James B. --- Wake Forest University School of Medicine
Opioid - Dopamine Interactions In Primate Cocaine Abuse

De Wit, Harriet --- University of Chicago
Drug Abuse and Impulsivity: Human Laboratory Models

Delgado, Melvin --- Boston University
Boston University Social Work Minority Research Center

Des Jarlais, Don C. --- Beth Israel Medical Center
National Study of Syringe Exchange Programs

Devi, Lakshmi A. --- New York University School of Medicine
Post-Translational Regulation of Opioid Receptors

Dobs, Adrian S. --- Johns Hopkins University
Gonadal Hormones on Body Composition, HIV and Drug Use

Donohew, Lewis --- University of Kentucky
Persuasive Strategies for Effective Anti-Drug Messages

Dutta, Aloke K. --- Wayne State University

Dopamine Transporter Agents Against Cocaine Dependence

Edlin, Brian R. --- University of California
Hepatitis C Virus Transmission In Crack Cocaine Smokers

Edlin, Brian R. --- University of California
Clinical & Histologic Spectrum of HCV Liver Disease In IDUs

Ellinwood, Everett H. --- Duke University Medical Center
Cocaine Withdrawal: A Window of Treatment Opportunity

Filizola, Marta --- Moltech Corporation
Methods to Identify New Ligands for Opioid Receptors

Fischman, Marian W. --- Research Foundation for Mental Hygiene
Novel Pharmacotherapies for Cocaine Dependence

Flynn, Brian S. --- University of Vermont
Youth-Focused Media To Prevent Substance Use

Follette, William C. --- University of Nevada -- Reno
The Therapy Relationship and Anxiolytic Dependence

Frankfurt, Oskar S. --- Apostain, Inc.
A Novel Apoptosis Assay With Antibodies To SSDNA

Garvey, Arthur J. --- Harvard School of Dental Medicine
Individualizing Treatment For Addicted Smokers

Gelernter, Joel E. --- VA Connecticut Healthcare System
Genetics of Cocaine Dependence

George, Frank R. --- Amethyst Technologies, Inc.
Science Education: Neurobiology For Practitioners

George, John S. --- Los Alamos National Lab
Mapping Brain Function By Combined MRI, MEG and fMRI

Gevins, Alan A. --- Sam Technology, Inc.
Neurocognitive Measurement System for Marijuana Research

Ghasemzadeh, Mohammadhossein --- Medical University of South Carolina
Glutamate Receptor and Chronic Cocaine

Gomez, Felipe --- Pennsylvania State University Hershey Medical Center
Conditioned Corticosterone and Drugs of Abuse

Grabowski, John --- University of Texas Medical School
Substance Abuse Medications Development Research Center

Greenlick, Merwyn R. --- Oregon Health Sciences University
National Clinical Trials Network: Northwest Node

Griffiths, Roland R. --- Johns Hopkins University
Licit & Illicit Abused Stimulant Drugs

Grigson, Patricia S. --- Pennsylvania State University
Drugs of Abuse and Learned Aversions: Solving A Paradox

Grillon, Christian ---Yale University
Anxiety, Disinhibition, and Risk for Drug Abuse

Halkitis, Perry N. --- New Jersey City University
Protease Inhibitor Adherence Among Drug Users

Hanlon, Thomas E. --- Friends Research Institute, Inc.

Incarcerated Addict Mothers and Their Children

Hansen, William B. --- Tanglewood Research, Inc.
Drug Abuse Prevention Tool Kit for Community Groups

Harrison, Murelle G. --- Southern University and A&M College
Preventing Substance Use In Rural African-American Youth

Hatsukami, Dorothy K. --- University of Minnesota
Tobacco Exposure Reduction

Hayes, Steven C. --- University of Nevada
Treatment of Nicotine Dependent Smokers

Heimer, Robert --- Yale University School of Medicine
Simulating HIV-1 Transmission Risks Among IDUs

Heller, Craig H. --- Stanford University Dept. of Biological Sciences
A High-Throughput Assay for Genetic Studies of Sleep

Henggeler, Scott W. --- Medical University of South Carolina
Randomized Clinical Trial of Juvenile Drug Court and MST

Higgins, Stephen T. --- University of Vermont
Treating Cocaine Abuse: A Behavioral Approach

Ho, Wenzhe --- Children's Hospital of Philadelphia
Drug Abuse, Substance P And HIV

Hoffman, Jeffrey A. --- Danya International, Inc.
Smoking Cessation Intervention For Youth

Hoffman, Jeffrey A. --- Danya International, Inc.
Performance Measurement For Treatment Improvement (PMIT)

Hoffmann, John P. --- National Opinion Research Center
Drug Use and Economic Productivity

Hovorka, George B. --- Talking Lights Co.
Visible Light Patient Information/Tracking System

Howlett, Allyn C. --- Saint Louis University
Cannabinoid Receptor Structure Activity Relationships

Hser, Yih-Ing --- UCLA Drug Abuse Research Center
Drug Abuse: Epidemiology, Treatment Process, & Outcomes

Huffman, John W. --- Clemson University
Synthesis of Cannabinoids, Analogues and Metabolites

Hurd, Yasmin L. --- Karolinska Hospital
Molecular Effect of Drug Abuse On Human Neurodevelopment

Inciardi, James A. --- University of Delaware
Ongoing Studies of Treatment for High Risk Drug Users

Jackson, Michel T. --- Sensimetrics Corporation
Course Software In Articulation and Phonology

Jacob, Howard J. --- Medical College of Wisconsin
Rat Genome Database

Jewett, Don L. --- Abratech Corporation
G-Wave Equipment To Detect Specific Language Impairment

Johnson, Bankole A. --- University of Texas

Lab Trials To Develop Medications For Cocaine Dependence

Johnson, C. A. --- University of Southern California
Transdisciplinary Tobacco Use Research Center

Johnson, Rolley E. --- Johns Hopkins University
Methadone and Buprenorphine: Ante- And Post-Partum

Johnson, Wendell --- Emory University
Late Onset Crack Use

Kanouse, David E. --- RAND
HIV Prevention for Crystal Methamphetamine Users

Kaplan, Stanley A. --- Drugabuse Sciences, Inc.
Naltrexone IM Depot for Treatment of Heroin Addicts

Karlson, Kevin W. --- Lifetechniques-I,Lp.
Electronic Smoking Cessation Monitor and Communicator

Kaskutas, Lee A. --- Alcohol Research Group
Cost-Effectiveness of HMO Residential & Outpatient Care

King, Chi-Hsin R. --- Albany Molecular Research, Inc.
Synthesis of 18-Methoxycoronaridine Hydrochloride

Kinsley, Craig --- University of Richmond
Pregnancy & Neural & Behavioral Plasticity In the Female

Kleber, Herbert D. --- New York State Psychiatric Institute
A Study of Anesthesia-Assisted Heroin Detoxification

Kleber, Herbert D. --- Research Foundation for Mental Hygiene Inc.
Novel Medication Approaches For Substance Abuse

Klein, Robert S. --- Montefiore Medical Center
Natural History of HCV Infection In Drug Use

Kosten, Thomas R. --- VA Medical Center
Cocaine Pharmacotherapies for Comorbid Populations

Kouri, Elena M. --- McLean Hospital/Harvard Medical School
Nicotine's Effects on Other Drugs of Abuse

Kreek, Mary J. --- Rockefeller University
Addictions: Genotypes, Polymorphisms, and Function

Lai, Shenghan --- Johns Hopkins University School of Hygiene and Public Health
Subclinical Atherosclerosis In HIV+ Black Cocaine Users

Lamb, Richard J. --- University of Texas Health Sciences Center
Increasing Contingency Management Success Using Shaping

Langberg, Edwin --- Sensor Electronics, Inc
Efficient Tactor For Tactile Aids

Lattimore, Pamela K. --- Research Triangle Institute
Comparison of Alternative Coercive Drug Treatment Models

Lee, Nancy M. --- California Pacific Medical Center
Non-Opioid DNA: Molecular/Cellular/Physiological Studies

Lerman, Caryn E. --- Georgetown University
Transdisciplinary Tobacco Use Research Centers

Leslie, Frances M. --- University of California, Irvine

Center on Tobacco Use Susceptibility and Intervention

Leukefeld, Carl G. --- Center On Drug/Alcohol Research
Enhancing Drug Court Retention In A Rural State

Li, Ming D. --- University of Tennessee
Mapping of Susceptibility Loci For Nicotine Dependence

Liddle, Howard A. --- University of Miami
Transporting Family Therapy To Adolescent Day Treatment

Liguori, Anthony --- Wake Forest University School of Medicine
Sleep Deprivation and Alcohol Effects In Marijuana Users

Ling, Walter ---Friends Medical Sciences Research Center
Medication Development Unit For Stimulant Dependence

Ling, Walter --- UCLA Drug Abuse Research Center
National Drug Abuse Treatment Clinical Trials Network: Pacific Node

Lipkin, Ian --- University of California
Microbial & Immune Factors--Treatment Resistance Cocaine Addiction

Lochman, John E. --- University of Alabama
Indicated Prevention Of Substance Use In High Risk Boys

Loew, Gilda H. --- Molecular Research Institute
Pharmacochemical Studies of Opiate Narcotics

Magura, Stephen --- National Development & Research Institute, Inc.
Group Motivational Intervention In Drug Abuse Treatment

Maidment, Nigel T. --- University of California, Los Angeles
Role of Endogenous Opioids In Heroin Abuse

Marlowe, Douglas B. --- Treatment Research Institute
The Role of Judicial Status Hearings In Drug Court

Meaney, Michael --- McGill University
Individual Differences In Maternal Care In The Rat

Meisch, Richard A. --- University of Texas Medical School
The Economics of Polydrug Abuse

Mendelson, Jack H. --- McLean Hospital
Biobehavioral Studies of Narcotics Abuse

Miller, Maureen --- National Development & Research
Networks, Resources and Risk Among Women Drug Users

Miller, William R. --- University of New Mexico
Moving Motivational Interviewing Into Practice

Moss, Andrew R. --- University of California
HIV and Hepatitis In Young Injectors: A Community Study

Musto, David F. ---Yale University
Previous American Drug Experience & Future Perspectives

Muthuswamy, Jitendran --- Infinite Biomedical Technologies
Imicroelectromechanical Precision Drug Delivery

Napier, T. Celeste --- Loyola University
Opioids and the Physiology of the Ventral Pallidum

Nelson, Agatha P. --- University of Virgin Islands

Socialization, Risk Perception And Drug Use In VI Youth

Nelson, Kenrad --- Johns Hopkins University
The Epidemiology of Hepatitis C Infection in Thailand

Neumeyer, John L. --- National Pharmacia International, Inc.
Dopamine Agonists for the Therapy of Cocaine Addiction

Nunes, Edward V. --- Research Foundation for Mental Hygiene, Inc.
Behavioral Therapy For Depression In Drug Dependence

Olney, John W. --- Washington University
Developmental Brain Damage By Drugs of Abuse

O'Malley, Stephanie S. --- Yale University
Tobacco Dependence and Risk Factors for Treatment Failure

Passik, Steven D. --- Indiana Community Care, Inc.
Aberrant Drug Taking & Untreated Pain In Cancer and AIDS

Patterson, Thomas L. --- University of California
Promoting Safer Sex In HIV+ MSM Methamphetamine Users

Picker, Mitchell J. --- University of North Carolina @ Chapel Hill
Biobehavioral Actions of Partial Mu Agonists

Pierce, Robert Christopher --- Boston University School of Medicine
Neurotrophins and Repeated Cocaine

Pomerleau, Ovide F. --- University of Michigan
Differentiation of Phenotypes for Smoking

Porreca, Frank F. --- University of Arizona
Spinal Dynorphin and Opioid Tolerance

Porrino, Linda J. --- Wake Forest University
Regional Brain Activation During Cocaine Abstinence

Prendergast, Michael L. --- University of California
Evaluating Voucher-Based Contingencies In A Drug Court

Rajah, Valli --- Columbia University
Partner Abuse & HIV-Risk Resistance of Women In MMPTS

Rao, Mahendra S. --- University of Utah
Genes Involved In Long Term Neural Plasticity

Raviv, Gabriel --- Bio-Logic Systems Corporation
Screening Device For Detecting Small Acoustic Tumors

Reith, Maarten E. --- University of Illinois College of Medicine
Cocaine and Regulation of the Dopamine Transporter

Resnick, Heidi S. --- Medical University of South Carolina
Prevention of Postrape Psychopathology and Drug Abuse

Riley, William T. --- Personal Improvement Computer Systems
Computerized Scheduling of Nicotine Nasal Spray

Roberts, Laura W. --- University of New Mexico, Health Sciences Center **Stigma & Rurality: Drug Abuse, HIV/STD & Mental Illness**

Roby, Richard J. --- Combustion Science & Engineering, Inc.
A Smoke Detector Alert Device for the Deaf

Roerig, Sandra C. --- Louisiana State University Medical Center

Spinal Nitric Oxide In Chronic Inflammatory Pain

Roman, Paul M. --- University of Georgia
Adoption Of Innovations In Private A&D Treatment Centers

Romich, Barry A. --- Prentke Romich Co.
Augmentative Communication Language Activity Monitor

Rosen, Bruce R. --- Massachusetts General Hospital
Functional Brain Mapping of Cocaine Action

Rounsaville, Bruce J. --- Connecticut Mental Health Center
Psychotherapy Development Research Center

Rowell, Peter P. --- University of Louisville School of Medicine
Functional Activity of Mesolimbic Nicotinic Receptors

Rudnick, Gary W. --- Yale University School of Medicine
Ion and Biogenic Amine Transport Mechanisms

Russell, Michael J. --- Aaken Laboratories, Inc.
Targeted Drug Delivery to the Brain

Sanudo-Pena, Clara M. --- Brown University
Motor Actions of Cannabinoids In A Parkinson's Model

Schafer, William --- University of California
Genetic Analysis of Nicotine Adaptation In C. Elegans

Schottenfeld, Richard S. --- Connecticut Mental Health Center
Counseling Conditions For Thrice Weekly Buprenorphine In A PCC

Schottenfeld, Richard S. --- Connecticut Mental Health Center
Brief Introductory Treatment For Demoralized Patients

Schottenfeld, Richard S. --- Connecticut Mental Health Center
Combining Behavioral Treatments With Agonist Maintenance

Schuster, Charles R. --- Wayne State University
High Doses of Methamphetamine on Human Brain Function

Sharma, Shubh D. --- Palatin Technologies, Inc.
Novel Metalopeptides As Opioid Analgesics

Shillingburg, Craig P. --- Integra Innovations, Inc
Rx System For Aged With Visual Impairment

Shoham, Varda --- University of Arizona
Family Consulation For Change-Resistant Smokers

Silverman, Kenneth --- Johns Hopkins Bayview Medical Center
A Reinforcement-Based Therapeutic Workplace

Simpson, D. D. --- Texas Christian University
Transferring Drug Abuse Treatment and Assessment Resource

Singer, Lynn T. --- Case Western Reserve University
Cocaine-Exposed Children and Anemia

Smith, James E. --- Wake Forest University
Drug Abuse & Neurotransmitter Receptor Autoantibodies

Smith, Miles P. --- Zebra Pharmaceuticals
Novel GBR Analogs for the Treatment of Cocaine Abuse

Smith, Miles P. --- Zebra Pharmaceuticals

Novel Bicyclic Analogs for Treatment of Cocaine Abuse

Stahler, Gerald J. --- Temple University
Cocaine Tx For Homeless Women: Community Support (CRA)

Stein, Elliot A. --- Medical College of Wisconsin
Functional MRI of Human Drug Abuse

Sterns, Ronni S. --- Creative Action, Inc.
De-Use System: An Intervention Product For Schools

Stitzer, Maxine L. --- Johns Hopkins Bayview Medical Center
Parametric Studies of Drug Abuse Abstinence Incentives

Stone, T. Howard --- University of Texas
Human Prisoners As Human Subjects In Therapeutic Research

Strauss, Shiela M. --- National Development & Research Institute
Drug Users' Self-Reported HIV Status: Validity/Methods

Sulk, Roberta A. --- CCtechnology
Low Risk Illicit Drug Level Monitoring

Sun, Lena Sy --- Columbia University
Cardiotoxicity After Maternal Cocaine Exposure

Surmeier, Dalton J. --- Northwestern University Medical School
Dopaminergic Signaling In the Nucleus Accumbens

Tang, Alice M. --- Tufts University
Nutritional Status of HIV Infected Injection Drug Users

Thiele, Dwain L. --- University of Texas Southwest Medical Center at Dallas
Opioid Metabolism By Immune System Peptidases

Thomas, David L. --- Johns Hopkins University
Hepatitis C Pathogenesis & the Human Genome

Tien, Allen Y. --- Medical Decision Logic, Inc.
Web-Based Client-Server Alcohol & Drug Abuse Assessment

Tien, Allen Y. --- Medical Decision Logic, Inc.
A Tool For Network Research On HIV Among Drug Users

Toga, Arthur W. --- University of California, Los Angeles
A Multimodal Multidimenstional (4D) Map of the Mouse Brain

Toll, Lawarence R. --- SRI International
Identifying Opioid Tolerance & Dependence-Related Genes

Tortu, Stephanie --- National Development & Research Institute, Inc.
Women Drug Users, Their Male Partners And HIV Risk

Trudell, Mark L. --- University of New Orleans
Novel Nicotinic Receptor Mediated Therapeutic Agents

Tsuang, Ming T. --- Massachusetts Mental Health Research Corp.
Molecular Genetics of Heroin Dependence

Turner, R. Jay --- Florida International University
Physical Disability, Mental Health and Substance Use

Victor, Ronald G. --- University of Texas Southwest Medical Center at Dallas
Cocaine and Sympathetic Nerve Activity In Humans

Vilim, Ferdinand Sven --- Mount Sinai School of Medicine

Neural Basis of Behavioral Priming: Induction and Memory

Voie, Arne H. --- Spencer Technologies, Inc.
Doppler Ultrasound Cochlear Bloodflow Monitor

Volkow, Nora D. --- Brookhaven Sciences Associates
Studies In Cocaine Abusers

Volpicelli, Joseph R. --- University of Pennsylvania
Innovative Approaches For Cocaine Pharmacotherapy

Wachtel, Stephen R. --- University of Chicago
Blockade of Methamphetamine Subjective Effects In Humans

Wagner, Glenn --- RAND
Adherence to HAART In the Context of Drug Abuse

Watkins, David I. --- Wisconsin Regional Primate Research Center
Study of MHC & CTL In Opiate-Dependent Monkeys With AIDS

Wechsberg, Wendee M. --- Research Triangle Institute
Pretreatment for African American Crack Abusers

Wehner, Jeanne M. --- Keystone Symposia
Genetics of Alcohol and Substance Abuse

Weisner, Constance --- Kaiser Foundation Research Institute
Long-Term Impact of Drug Treatment on Outcome & Cost

Wenzel, Suzanne L. --- RAND
Collaborative Linkages: Drug Courts & Service Providers

Wenzel, Suzanne L. --- RAND
Drug Abuse, Violence, and HIV/AIDS In Impoverished Women

White, Francis J. --- Chicago Medical School
Cocaine Addiction and Neuronal Excitability

Winger, Gail D. --- University of Michigan
Stimulants, Depressants & Hallucinogens As Reinforcers

Wolf, Marina E. --- Chicago Medical School
Dopamine/Glutamate Interactions In Nucleus Accumbens

Woody, George E. --- University of Pennsylvania
Clinical Research Cooperative

Woody, George E. --- University of Pennsylvania
Persistent Effects of LT/LI Drug Risk Counseling

Xu, Xiping --- Harvard School of Public Health
Genetics of Nicotine Addiction Vulnerability

Yeomans, David C. --- University of Illinois
Development of a Primate Behavioral Nociceptive Assay

Yu, Lei --- University of Cincinnati
Mu Opioid Receptor Gene In Heroin Addicts

Yu, Xiao-Fang --- Johns Hopkins University
Behavioral and Virologic Features of HIV+ IDUs In China

Zimmerman, Marc A. --- University of Michigan
A Longitudinal Study of School Dropout and Substance Use

Zink, M. Christine --- Johns Hopkins University

Effects of Cocaine On SIV AIDS & CNS Disease

[Office of the Director][Report Index][Next Report Section]

Archive Home | Accessibility | Privacy | FOIA (NIH) | Current NIDA Home Page

National Institute on Drug Abuse

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

February, 2000

Review Activities

Grant/Contract Reviews

OEPR organized and managed thirteen grant review committees and subcommittees in this cycle. These included the chartered meetings: Treatment Review, Health Services Review, Training and Career Development Review, and the Medication Development Review. In addition, review meetings for Centers, Program Projects, the Strategic Program for Innovative Research on Cocaine (and Other Psychomotor Stimulants) Addiction Pharmacotherapy (SPIRCAP), B-START, and Minority Institutions Drug Abuse Research Development Program were organized and managed.

Contract reviews were held for a number of NIDA initiatives. Reviews for the Archway Drug Treatment Clinic, which supports services at the Intramural Research Program, were completed, as were reviews for a contract to provide technical and logistical support assistance for the NIDA Center on AIDS and Other Medical Consequences (CAMCODA) and a contract to provide support for the International Visiting Scientist and Technical Exchange (INVEST) Fellowships. Reviews were held in January for the Small Business Innovation Research (SBIR) program. NIDA announced interest in receiving SBIR proposals in the following thirteen areas, and proposals were received in response to twelve of the topics:

- Drug Supply Services Support
- Chemical Libraries for Drug Development
- Analytical Techniques Program
- Computerized Neuropsychological Testing Software
- Development of Improved HIV Risk Behavior Questionnaire
- Develop Prevention Research Dissemination
- Design and Construction of a Multi-environment, Multi-choice Rodent Testing Apparatus
- Measurement Modules for Prevention Interventions
- Web-Based Visualization and Analysis of DNA Micro-Array Data
- Kits for DNA Micro-Array Technology
- Antibodies for Neuroscience Research
- Telemedicine
- Prevention Training

Each topic requires a separate review meeting.

NIDA Referral Guidelines

Dr. Rita Liu, NIDA's Receipt and Referral Officer, completed the coordination and writing of new NIDA programmatic referral guidelines that provide guidance for the Center for Scientific Review as it determines which NIH Institute receives unsolicited applications and that clarifies areas of overlapping interest with other NIH Institutes. Representatives from all NIDA Offices and Divisions participated in the development of this document, in particular Drs. Charlie Sharp, Jamie Biswas, Meyer Glantz, Sandy Genser, Joe Frascella, Lisa Onken , and David Shurtleff made large contributions.

Updated FAQs

OEPR updated and expanded the Frequently Asked Questions (FAQs) for NIDA's web site. The FAQs cover a broader range of information than previously and are more comprehensive in addressing anticipated needs.

Updated PAs for R03 and P01

OEPR updated the NIDA wide program announcements for small grants (R03 mechanism) and the program and review guidelines for program projects (P01 mechanism). These updates clarify information for applicants, staff, and reviewers, consolidating the information in a single document.

OEPR Symposium Series

The OEPR Symposium Series, a forum for staff development, continued in September, October, and November. Major topics included receipt dates for application submissions, streamlined review procedures, supplements, and review integration. The series will continue in January. Dr. William C. Grace, Deputy Director, OEPR, manages the symposium series.

[Office of the Director][Report Index][Next Report Section]

Archive Home | Accessibility | Privacy | FOIA (NIH) | Current NIDA Home Page

National Institute on Drug Abuse

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

February, 2000

Congressional Affairs

(Prepared December 27, 1999)

NIH Funding for FY 2000

On November 29, 1999, the President signed the **Omnibus Appropriation Bill for FY 2000,** H.R. 3194 [P.L. 106-113] which includes funding for the National Institutes of Health. The final conference agreement on the FY 2000 Labor-HHS-Education appropriations bill, H.R. 3424, was included by cross-reference in the Consolidated Appropriations Act, H.R. 3194 [H. Rept. 106-479]. The House passed the appropriations package on November 18 and the Senate on November 19, 1999.

The conference agreement provides **$17.913 billion for the NIH,** an increase of $2.3 billion (14.7 percent) over FY 1999. The conference agreement provides funding of **$689.4 million for NIDA,** an increase of $81.5 million (13.4 percent) over FY 1999.

In an effort to stay within the spending caps and avoid using the Social Security surplus the final conference agreement includes a 0.38 percent across-the-board cut of all discretionary spending and a delay in obligations until September 29, 2000, for significant portions of various program budgets, including NIH, CDC, and HRSA.

Selected Conference Bill Language:

Transfer authorities: remain consistent with FY 1999 appropriation language. The Director, NIH, may transfer up to 1% of any appropriation (OD); HHS may transfer between appropriations up to 1% of any discretionary funds, but it may not increase any single appropriation by more than 3% (sec. 206); The Director, NIH, and the Director, OAR, may transfer up to 3% of funds identified as HIV/AIDS (sec. 207).

Delayed obligations: $3 billion of NIH funds are not available for obligation until September 29, 2000; delayed funds are available until October 15, 2000, pending policy decision (sec. 216).

Reduction to be taken: $17.9 billion Conference Mark does not reflect the across-the-board spending cut of 0.38%.

OD: OAR, $44.953 million; Foundation for NIH: $500,000.

NIAID transfer: Requires transfer of $20 million from NIAID to CDC by January 15, 2000 for the study of the safety and efficacy of vaccines used against biological agents (sec. 221).

Challenge grant program: $20 million earmarked for NIH in Public Health and Social Services Emergency Fund in the Office of the Secretary (no change from Senate report).

NIH Office of the Director

Minority Programs: Minority Access to Research Careers, Minority Biomedical Research Support, Research Centers in Minority Institutions, and the Office of Research on Minority Health programs should continue to be supported at a

level commensurate with their importance.

Parkinson's Disease: NIH is requested to develop a report to Congress by March 1, 2000 outlining a research agenda for Parkinson's focused research for the next five years, along with professional judgment funding projections. The NIH Director should be prepared to discuss Parkinson's focused research planning and implementation for FY 2000 and FY 2001.

Biomedical imaging and engineering: NIH is urged to establish an Office of Bioimaging/Bioengineering and to review the feasibility of establishing an Institute of Biomedical Imaging and Engineering. The Office should coordinate imaging and bioengineering research activities, both across the NIH and with other Federal agencies. The NIH shall report to the Appropriations Committees of the House and Senate on the progress achieved by this Office no later than June 30, 2000.

ORMH: The Office of Research on Minority Health is encouraged to expand and strengthen science-based HIV prevention research for a wide range of minority populations.

House Appropriations Committee Report Language for the National Institute on Drug Abuse [HRpt. 106-370]

Centers for Drug Abuse Research and Treatment: The Committee commends NIDA for its strategy of developing and establishing centers for drug abuse research and treatment around the country. Consideration should be given to locating one or more centers in areas where drug trafficking, the production of illegal drugs such as methamphetamine, and drug abuse is more prevalent.

Children and Adolescents: Recognizing the devastating impact of drug addiction on children and youth, the Committee is pleased that NIDA has developed a children and adolescent research initiative. The Committee urges NIDA to work with other NIH Institutes to expand its research portfolio into areas of co-occurring mental disorders, developmental consequences, prenatal exposure, genetic vulnerability, and environmental protective and risk factors. This type of research offers hope of improved prevention of initial drug use and prevention of the health consequences of addiction.

Clinical Trials: The Committee is pleased with NIDA's continuing progress in developing behavioral and pharmacological drug abuse treatments and supports NIDA's new treatment initiative to establish a National Drug Abuse Treatment Clinical Trials Network designed to test the efficacy of promising pharmacological and behavioral treatments through large-scale clinical trials. The Committee is also pleased with NIDA's leadership in forging strong partnerships with treatment researchers and community-based treatment providers as a means of assuring that effective new treatments will be tested in real-life settings and incorporated into ongoing community-based drug treatment programs.

Genetic Vulnerability: Genetics and the environment are two factors that influence drug abuse and addiction. The relationship between the two is complex, requiring continued research in areas of behavioral genetics, psychiatric and epidemiological genetics, molecular genetics, and population genetics. The Committee encourages NIDA to expand its development of research for improving prevention and treatment interventions in this area. Hepatitis C: The Committee commends NIDA for participating in the trans-Institute request for applications for Hepatitis C and urges enhanced research in this area consistent with the recommendations made by the Hepatitis C Consensus Development Conference.

Medications Development: The Committee encourages NIDA to study the development of anti-addiction medications to clarify the neurological and behavioral benefits of the use of various pharmacological agents and to continue to develop an understanding of how physicians can best utilize these medications. NIDA is also encouraged to expand its support for research to develop medications that are specifically geared to the needs of varied populations as well as research on treatment approaches for application to poly-drug addiction.

Neuroscience: Basic neuroscience provides a foundation for NIDA's research portfolio. The Committee urges NIDA to continue efforts to develop new areas of research in neuroscience and commends NIDA's support for continued research and dissemination of information to the public on the neurobiology of drug addiction to specific drugs of abuse.

Nicotine Research: The Committee recognizes that the health consequences of nicotine addiction are substantial to adults, children, and adolescents and applauds the gains NIDA has made in supporting research that has yielded effective replacement therapies and behavioral interventions. The Committee encourages NIDA to continue to develop research on the prevention, behavioral, and pharmacological treatment of nicotine addiction. The Committee also

supports NIDA's ongoing research in the basic sciences, behavioral and medical treatments, and epidemiology of nicotine use and abuse.

Senate Appropriations Committee Report Language for the National Institute on Drug Abuse [SRpt. 106-166]

Methamphetamine: The Committee is very disturbed by the explosion in methamphetamine abuse across the nation. The problem is especially acute in Iowa and other Midwestern states. The Committee urges NIDA to expand its research on improved methods of prevention and treatment of methamphetamine abuse and expects to be briefed on these efforts by December 1, 1999.

Behavioral Science: The Committee understands that behavioral intervention is a critical element in halting drug abuse. The Committee continues to support NIDA's expansion of its behavioral science portfolio and views NIDA as a model of how to approach its behavioral science and public health responsibilities.

Neuroscience: The Committee recognizes that basic neuroscience provides a foundation for NIDA's research portfolio. Basic neuroscience research has advanced the field's understanding of drug abuse and addiction. The Committee urges NIDA to continue its efforts to develop new areas of neuroscience research.

Genetic Vulnerability: The Committee understands that both genes and environment influence drug abuse and addiction. The relationship between the two is complex, requiring continued research in areas of behavioral genetics, psychiatric and epidemiological genetics, molecular genetics, and population genetics. The Committee encourages NIDA to expand its development of this area of drug and addiction research.

Children and Adolescents: Recognizing the devastating impact of drug addiction on children and youth, the Committee commends NIDA's children and adolescent research initiative. The Committee urges NIDA to expand its research portfolio in areas of co-occurring mental disorders, developmental consequences, prenatal exposure, genetic vulnerability, and environmental risk factors.

Hepatitis C: Language similar to House Report.
Clinical Trials: Language similar to House Report.
Medications Development: Language similar to House Report.
Nicotine Research: Language similar to House Report.

Hearings/Briefings of Interest

September 9, 1999 - **Scientific Research on Addiction** - Dr. Frank Vocci, Director, Division of Treatment Research and Development, NIDA, briefed Marcia Lee, staffer to Senator Joseph Biden (D-DE), Ranking Member, Senate Judiciary Subcommittee on Youth Violence, at her request. The briefing, before Ms. Lee and other staffers, was to discuss S. 486, the Methamphetamine Anti-Proliferation Act of 1999 and focused on current addiction research. Representatives from SAMHSA, the Drug Enforcement Agency, and the Department of Health and Human Services were also in attendance.

October 8, 1999 - **NIDA Research Programs** - Dr. Timothy Condon, Associate Director, NIDA, briefed Sharon Pinkerton, majority staffer on the House Government Reform Subcommittee on Criminal Justice, Drug Policy, and Human Resources (John Mica, R-FL, Chair) on current NIDA research programs. Ms. Pinkerton, new to the Subcommittee, discussed a wide-range of initiatives with Dr. Condon.

October 21, 1999 - **ONDCP Youth Media Campaign** - The House Appropriations Subcommittee on Treasury, Postal Service, and General Government (Rep. Jim Kolbe, R-AZ, Chairman) held a hearing on Phase III of the Office of National Drug Control Policy's Youth Anti-Drug Media Campaign. Susan David, M.P.H., testified before the Subcommittee on efforts to track the effectiveness of ONDCP's outreach campaign to combat youth drug use. The Subcommittee also heard testimony from General Barry McCaffrey, Director, ONDCP, and representatives from the entertainment and marketing industry.

November 15, 1999 - **Field Hearing on Regional Drug Abuse** - Dr. Alan Leshner, Director, NIDA testified at a field hearing in Newcastle, DE, that focused on the region's persistent substance abuse problems. At the hearing, held by Senators Joseph Biden (D-DE) and Arlen Spector (R-PA), Dr. Leshner spoke on the impact of drug use, particularly heroin, on brain function, as well as misperceptions surrounding the snorting of heroin and addiction.

Bills of Interest

H.R. 2634 - Drug Addiction Treatment Act of 1999 - On September 13, 1999, the House Commerce Subcommittee on Health and Environment held a mark-up session on H.R. 2634. This bill was introduced on July 29, 1999, by Representative Tom Bliley (R-VA) as the Drug Addiction Treatment Act of 1999, which would amend the Controlled Substances Act with respect to registration requirements for practitioners who dispense narcotic drugs in schedule IV or V for drug addiction treatment. The bill would allow qualified physicians, as determined by DHHS, to prescribe schedule IV and V anti-addition medications in physicians' offices without an additional DEA registration if certain conditions are met. These include certification by participating physicians that they are a physician licensed under state law; they are trained to treat opiate abuse; they have the capacity to refer patients for counseling and other appropriate ancillary services; the total number of patients shall not exceed a specified number unless the Secretary HHS adjusts the number. Other key provisions include the following: the drug involved must be approved by the FDA for use in maintenance or detoxification treatment and must not have been the subject of an "adverse determination;" if a physician dispenses a narcotic drug in Schedule IV or V in violation of this law, a practitioner may lose his registration with DEA; during the first 3 years either the Secretary or the Attorney General may make a determination that the law should not remain in effect; states can overrule the 3 year grace period with their own legislation if they deem this appropriate. On July 30, 1999, the House Commerce Subcommittee on Health and Environment (Chairman Bilirakis, R-FL) held a hearing on H.R. 2634. A similar measure (S. 324) was introduced in the Senate on January 28, 1999, by Senator Orrin Hatch (R-UT), and referred to the Senate Committee on the Judiciary.

S486/S324 - S 486 was introduced by Sen. Ashcroft (R-MO) on Feb. 25, 1999. The Senate passed S486 by voice vote Nov. 19, 1999. A substitute amendment was added from other drug legislation (HR1428) which was designed to increase the availability of treatment and a provision similar to S324 and HR2634, that would allow certain physicians to prescribe schedule III, IV, and V anti-addiction medications for heroin addiction without additional DEA registration (see HR2634 above). S486, as passed by the Senate, aims to deter the production and distribution of methamphetamine. The measure would increase funding authorizations for federal, state and local law enforcement organizations, prohibit the posting of methamphetamine drug recipes on the Internet -- which are now readily available -- and stiffen penalties for illegal production of the drug. The legislation would authorize $30 million for the Drug Enforcement Administration (DEA) each year through 2004 to train, assist and deploy agents; $25 million per year for law enforcement to combat the drug's use and distribution in "high-intensity trafficking areas;" and $25 million per year for prevention, interdiction and studies of the law's effectiveness.

H.R. 2130/S1561 - Date Rape Prevention Act - Passed by the House on October 12, 1999. Sponsored by Fred Upton, R-MI, this bipartisan bill aimed at curbing the abuse of three sedatives that have emerged as so-called "date rape" drugs, was approved August 5, 1999 by the House Commerce Committee. The measure would add GHB (gamma hydroxybutyric acid, also known as Liquid Ecstasy) and GBL (gamma butyrolactone, a primary component of the GHB) to Schedule I, and ketamine to Schedule III of the Controlled Substances Act. The legislation also would require the Justice Department to assist with the development of forensic tests to detect the ingestion of GHB or related substances; direct the HHS Secretary to submit annual reports to Congress estimating the number of sexual assault cases involving date-rape drugs; and require the HHS Secretary to develop a national awareness campaign to educate people about the dangers of date-rape drugs and the strong CSA criminal penalties that could be imposed on those who abuse them. The Senate on Nov. 19, 1999, stripped the language from the House-passed bill, and inserted the text of S1561, before passing HR2130 and sending it back to the House.

S. 1561 - The Date Rape Control Act of 1999 - On November 18, 1999, the Senate Committee on the Judiciary (Orrin Hatch, R-UT, Chairman) reported S. 1561 to the Senate with no written report. The next day the Senate passed H.R. 2130 in lieu of S. 1561, after amending it to contain the language of S. 1561. The bill, introduced on August 5, 1999 by Senator Spencer Abraham (R-MI) proposed to amend the Controlled Substances Act to require the Attorney General to add gamma hydroxybutyric acid to Schedule I and ketamine to Schedule III. It also would require the Secretary of HHS to submit to Congress reports on the number of incidents of the abuse of date-rape drugs that occurred in the most recent 1 year period, and to develop a plan, in consultation with the Attorney General, for carrying out a national campaign to educate the public on the dangers of date-rape drugs. Finally, the Secretary of HHS would be required to establish an advisory committee to make recommendations to the Secretary on issues related to date rape.

S. 1947 - On November 17, 1999, Senator Orrin Hatch (R-UT) introduced legislation that would provide for an assessment of the abuse of and trafficking in gamma hydroxybutyric acid, flunitrazepam, ketamine and other so-called "club drugs" whose use has been associated with sexual assault. S. 1947 was referred to the Senate Committee on the Judiciary.

S. 976 - The Youth Drug and Mental Health Services Act - Passed by the Senate on November 13, 1999.

Originally introduced on May 6, 1999 by Sen. William Frist (R-TN) The Youth Drug and Mental Health Services Act, authorizes SAMHSA and introduces some new youth-related programs. On July 28, 1999 the bill was ordered reported by the full Senate Health, Education, Labor & Pensions Committee with an amendment in the nature of a substitute. Under the bill SAMHSA would end the practice of requiring states to expend a certain portion of federal funds on specified programs, but states would be required to file more comprehensive progress reports. The bill also would set up grant programs under SAMHSA to support: youth and adolescent substance abuse prevention and treatment initiatives; mental health initiatives designed to combat teen violence; mental health and substance abuse programs for the homeless; emergency funds for mental health and substance abuse needs; and treatment services for juvenile delinquents. The bill did not include a provision that would have permitted blending of substance abuse and mental health block grant funds without accountability for the purpose of servicing individuals diagnosed with co-occurring substance abuse and mental health disorders. Instead the bill restated current law. The Committee amended the bill by adopting a charitable choice provision that permits religious organizations to receive federal funds to provide alcohol and drug treatment and prevention services.

Congressional Schedule

The Senate adjourned *sine die* on November 19, 1999, and the House adjourned *sine die* on November 22, 1999. Both the House and Senate reconvened for the second session of the 106th Congress on January 24, 2000.

[Office of the Director][Report Index][Next Report Section]

Archive Home | Accessibility | Privacy | FOIA (NIH) | Current NIDA Home Page

National Institute on Drug Abuse

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

February, 2000

International Activities

NIDA Director, Dr. Alan I. Leshner, was awarded an honorary degree from the Pavlov Medical University, St. Petersburg, Russia, in an October **symposium marking the centenary of the Pavlov Medical University Department of Pharmacology**. Dr. Leshner presented a lecture on recent progress and emerging opportunities for understanding the biological, behavioral, and social mechanisms of drug abuse and addiction; the implications of this knowledge for prevention, treatment, and policy; and the goals for drug abuse and addiction research into the next millennium.

During October 1999, NIDA signed an **Exchange of Letters** with two research organizations in The Netherlands - the Netherlands Organization for Scientific Research and the Health Research and Development Council - agreeing to promote scientific collaboration and exchange in the fields of biomedical and behavioral research related to drug abuse. The letters were signed at an October **Binational Symposium on Drug Abuse and Addiction Research and Innovation**. During the symposium, NIDA Director, Dr. Alan I. Leshner, spoke on challenges and opportunities for drug abuse research, and Dr. M. Patricia Needle, International Program, addressed issues in international research collaborations. Workshop participants discussed biomedical and behavioral research on risk, resiliency, and vulnerability factors for drug abuse; principles of effective prevention programs; relapse and the role of craving; pharmacotherapies and behavioral models for drug abuse treatment; monitoring illicit drug use; and accessing hard-to-reach populations. Extramural researchers taking part included Hendricks Brown (University of South Florida), Stephen Higgins (University of Vermont), Kathleen Merikangas (Yale University), Richard Rawson (Matrix Center, Los Angeles), Terry Robinson (University of Michigan), and Claire Sterk (Emory University).

NIDA and the Spanish National Plan on Drugs cosponsored the **Second Cooperation Seminar on the Evaluation of Drug Abuse and HIV/AIDS Prevention Activities**, held during September 1999 in Madrid. Speakers reported on current prevention programs in the United States and Spain; research methods to evaluate prevention programs, local needs, and community programs; ethnographic research methods; assessing the effectiveness of prevention interventions for high-risk adolescents; and opportunities for binational collaborative research. The U.S. delegation included: Dr. M. Patricia Needle, International Program; Dr. Richard Clayton, University of Kentucky; Dr. Merrill Singer, Hispanic Health Council, Hartford, Connecticut; Dr. Claire Sterk, Emory University, Atlanta; Dr. Richard H. Needle, CAMCODA; and Ms. Susan L. David, DESPR.

Dr. M. Patricia Needle, International Program, traveled to Baltimore, MD, in September and October 1999 to meet with the 1999-2000 Hubert H. Humphrey Fellows at The Johns Hopkins University to discuss opportunities for NIDA professional affiliations with extramural researchers. In December 1999, the NIDA International Program hosted an **orientation program for the Humphrey Fellows**. NIDA participants included Mr. Richard A. Millstein, Deputy Director, NIDA; Drs. Henry (Skip) Francis and Richard H. Needle, CAMCODA; Dr. Nancy Pilotte, DNBR; Dr. Peter Delany, Larry Seitz, Ms. Susan David, and Ms. Moira O'Brien, DESPR; Dr. Frank Vocci, DTR&D; and Dr. M. Patricia Needle, International Program.

The **1999-2000 NIDA INVEST Fellows have begun their postdoctoral research in the United States**. Dr. Vaughan Rees, Australia, will investigate whether alcohol abuse and stage of motivational change among in-treatment injection drug users are significantly related to HIV risk behaviors. He will work with Dr. Jeffrey Samet, Boston University School of Medicine. Dr. Abdel Assi, Egypt, will use hippocampal brain slices from guinea pigs to

investigate whether opioids produce their cognitive and analgesic effects by causing presynaptic inhibition of neurotransmitter release. Dr. Assi is working with Dr. Charles I. Chavkin, University of Washington. Dr. Elisa Mengual, Spain, will use electron microscopic immunocyto-chemical localization of transporters and receptors to study the cellular substrate for physiological interactions of dopamine, which has been implicated in the rewards produced by various drugs of abuse. Her Fellowship mentor is Dr. Virginia M. Pickel, Will Medical College, Cornell University.

Mr. Richard A. Millstein, Deputy Director, NIDA, represented the United States at the U.S.-U.K. Drug Summit in meetings with the U.K. Drugs Prevention Advisory Service, Home Office, and the U.K. Department of Health, London, England, October 24-26, 1999.

Mr. Richard A. Millstein, Deputy Director, NIDA, presented on "Epidemiology: A Tool to Guide Development of a Science-Based Drug Abuse Policy" at the European Monitoring Centre on Drugs and Drug Addiction, Lisbon, Portugal, October 28, 1999.

Dr. Svetlana Dambinova, Laboratory of Molecular Neurobiology, Institute of the Human Brain, Russian Academy of Sciences, St. Petersburg, consulted recently with NIDA and other NIH researchers at NIH headquarters and the NIDA Intramural Research Program in Baltimore, Maryland. Dr. Dambinova presented a seminar for U.S. scientists on the role of mu-delta opiate receptors in drug abuse diagnosis and treatment. Following her two-week working visit at the NIDA Intramural Research Program, Dr. Dambinova consulted with two NIDA-supported researchers: Dr. James Justice, Emory University; and Dr. James Smith, Wake Forest University.

Dr. Svetlana I. Chefer, Neuroimaging Research Branch, IRP, presented a poster entitled "Using Samples of Venous Blood to Calculate Metabolic Rates for Glucose with PET and FDG in Rhesus Monkeys" at the High Resolutions Imaging in Small Animals with PET, MR and Other Modalities Conference, Amsterdam, Netherlands, September 27-29, 1999.

Dr. Svetlana I. Chefer, IRP, presented a poster entitled "2-[18F]Fluoro-A-85380: A Novel Ligand for Imaging a4b2 Subtype of Nicotinic Receptors" at the Functional Imaging in Drug Discovery and Development, Centre Francais du Commerce Exterieur, Paris, France, September 30-October 1, 1999.

Dr. Alexey Mukhin, Neuroimaging Research Branch, IRP, presented a poster entitled "Radiohalogenated Analogs of A-85380, Novel Ligands for the Study of a4b2 Nicotinic Receptors" at the Neuronal Nicotinic Receptors Conference: From Structure to Therapeutics, Venice, Italy, October 1-4, 1999.

Dr. William J. Freed, Cellular Neurobiology Branch, IRP, introduced the topic and participated in the debate entitled, "Is there a future for neural tissue transplants?" at the Mexican Physiological Society meeting, Zacatecas, Mexico, on September 28, 1999, and presented a seminar entitled, "Neural Cell Lines: Applications and Methods," on October 1st at the Centro de NeurobiologRa, Universidad Nacional Aut—noma de Mexico in Juriquilla, QuerŽtaro Mexico. He also spent the week as a visiting scientist at the Centro de NeurobiologRa with Dr. Magda Giordano and fellow scientists and gave advice on scientific matters.

Dr. George Uhl, Molecular Neurobiology Branch, IRP, presented at the International Symposium on Transporters and Ion Channels (Shizuoka, Japan) and at the Brain Sciences Institute, Riken Institute (Tokyo Japan) during the last weeks of August, 1999.

Dr. Kenzie Preston, Treatment Branch, IRP, presented "Safety of Buprenorphine: Ceiling Effects on Subjective and Physiological Measures at High Intravenous Doses" at the annual scientific meeting of the International Council of Alcoholism and Addiction , Vienna, Austria, August, 1999.

Dr. Kenzie Preston, Treatment Branch, IRP, presented "Developments in the treatment of opioid abuse" in the NIDA-sponsored symposium, "New Directions in Substance Abuse Treatment," at the International Council of Alcoholism and Addiction annual scientific meeting, Vienna, Austria, August 1999.

Dr. Roy Wise, Behavioral Neuroscience Branch, IRP, gave an invited address at the 21st International Summer School of Brain Research held at the Netherlands Institute for Brain Research in Amsterdam in August 1999. The theme of this year's program was Cognition, Emotion, Autonomic Responses: The Integrative Role of the Prefrontal Cortex and Limbic Structures. Dr. Wise spoke on "Interactions Between Medial Prefrontal Cortex and Meso- Limbic Components of Brain Reward Circuitry.

Drs. David Gorelick, Clinical Pharmacology Section, and Charles Schindler, Preclinical Pharmacology Section of the NIDA IRP met on Dec. 1, 1999 with a group of scientists from the Russian State Research Institute of Organic Chemistry and Technology in Moscow. The meeting was to discuss possible research collaboration in the study of the enzyme butyrylcholinesterase as a treatment for cocaine addiction. The Russians' visit to the U.S. was sponsored and

organized by the Biotechnology Travel Grants Program of the US Civilian Research and Development Foundation for the Independent States of the Former Soviet Union, on behalf of the U.S. Department of State.

Dr. Steven Goldberg, Preclinical Pharmacology Section, IRP gave a presentation entitled, "Behavioral Interactions between Caffeine and Nicotine," at the Pharmacology, Biochemistry & Behavior 4th International Meeting entitled, "Drugs of Desire: Focus on Caffeine, Nicotine & Alcohol," Morzine, France, January 10-14, 2000.

The Fogarty International Center (FIC) has launched an international tobacco control research and training effort. The aim is to support and build upon the international tobacco control research efforts of other agencies within and beyond the Department of Health and Human Services (e.g., the CDC, SAMHSA, the WHO Tobacco Free Initiative, FDA, World Bank and others). NIH Institutes who have met with the FIC and other DHHS and Federal components include NIDA, NCI, NHLBI, NIMH, NIDCD, NIDCR and NICHD and OD (OBSSR). International training, outcome evaluation, and prevention research all are being aired as possible activities of this effort.

In October 1999, Dr. Dorota Majewska, DTR&D, visited the Addiction Treatment Center, National Institute of Psychiatry and Neurology, Warsaw Poland. During the visit she discussed with Dr. Karina Chmielewska and her colleagues certain novel pharmacotherapeutic strategies for the treatment of stimulant dependence, proposed by Dr. Majewska several years ago. They now have preliminary clinical data suggesting efficacy of piracetam combined with certain antidepressants in the treatment of amphetamine dependence. Currently NIDA is conducting a controlled trial with piracetam at the University of Pennsylvania. If a positive signal is detected, NIDA may proceed with the subsequent study combining piracetam with antidepressants. Because certain drugs (such as piracetam) are not available in the U.S. but are used in other European countries, the ability to conduct pilot/observational studies in other countries is of great value to NIDA research.

Mr. Nicholas Kozel, DESPR, cochaired a joint meeting of the East and South Asian Multi-City Epidemiology Work Group (AMCEWG) meeting held in Penang, Malaysia on November 1-4, 1999. The East and South Asian Work Group meeting was composed of researchers from Kuala Lumpur, Manila, Bangkok, Beijing, Hanoi, Taipei, Port Moresby, Colombo, Dhaka, and Madras. The project is funded by the Association of Southeast Asian Nations and is coordinated by the Universiti Sains Malaysia. A Consensus Statement produced at the meeting stated that heroin is the primary drug of abuse in both regions. Abuse of codeine and buprenorphine in India and Bangladesh and opium in Vietnam and the emergence of Tramidol abuse in China were also noted. Abuse of methamphetamines, which historically has been endemic in the Philippines, is spreading throughout much of East Asia and is becoming a major drug problem in the region. In addition, methamphetamine abuse has recently been reported as an emerging problem in Northern India. First indications of the appearance of cocaine in Papua New Guinea were also reported. Abuse of benzodiazepines, cannabis and inhalants continue at endemic levels throughout much of the region.

Mr. Nicholas Kozel, DESPR, represented NIDA in the biannual meetings of the South African Community Epidemiology Network on Drug Use (SACENDU) held in Johannesburg and Durban on October 5-7,1999. Alcohol is the dominant substance of abuse throughout the country, while cannabis and Mandrax (methaqualone) used alone or in combination (white pipe) are the major illicit drugs of abuse. Indicators of both availability and abuse of heroin and cocaine are beginning to increase noticeably, as well as club drugs, such as Ecstasy and LSD. In addition, abuse of over-the-counter and prescription drugs, including Rohypnol, continues to be an issue across sites.

Dr. Elizabeth Robertson, DESPR, met with Dr. Brian Pezzuti, Chair of Committees, Parliament of New South Wales on August 3, 1999 to discuss cross-cultural adaptation of prevention programming in the United States and Australia.

On November 2, 1999, Dr. Elizabeth Robertson, DESPR, met with Rita Azuje de Schlemo, Director of Prevention Division of Venezuela National Committee Against Illegal Drug Use. NIDA's research was of great interest to Ms. Azuje de Schlemo because Venezuela is attempting to establish prevention programming in school and neighborhood settings.

Dr. Elizabeth Robertson, DESPR, represented NIDA at the 2nd European Conference on Evaluation of Drug Prevention sponsored by the European Monitoring Centre for Drugs and Drug Addiction. The meeting took place on December 2-4, 1999 in Strasbourg, France.

Dr. William Cartwright, SRB, DESPR represented NIDA at the International Conference on Health and Economic Development, November 15-16, 1999 that was sponsored by the Fogarty International Center (FIC) of the National Institutes of Health (NIH) in consultation with the World Bank and World Health Organization.

Ms. Van-Ly Phan, a French INSERM graduate student working under Dr. Tangui Maurice on a joint project in collaboration with Dr. Steven Goldberg and Dr. Tsung-Ping Su of IRP, NIDA, spent two months in Dr. Su's laboratory from September 8 to November 8, 1999. Ms. Phan worked directly with Dr. Teruo Hayashi in Dr. Su's laboratory for cloning sigma-1 receptors from NG-108 cells and rat brains and producing sufficient amounts of full length sigma-1

receptor c-DNA. The cloned c-DNA will be used for studying the involvement of sigma-1 receptors in methamphetamine self-administration.

Dr. Tsung-Ping Su, NIDA, IRP, was invited to speak at a symposium on "Opioids and Physiological Roles" in an IUPHAR South East Asia Pacific Rim Meeting held in Taipei, Taiwan on November 4, 1999. The speech was entitled "Delta Opioid Peptide DADLE Promotes Cell Survival".

Dr. Tsung-Ping Su, NIDA, IRP, was invited to give a seminar at the National Cheng-Kong University School of Medicine in Tainan, Taiwan on November 10, 1999. The title of the seminar was "Delta Opioid Peptide DADLE Protects against Apoptosis in Neuronal Cells".

Dr. Tsung-Ping Su, NIDA, IRP, was invited on November 20, 1999 to present at a special Memorial International Symposium celebrating the 50th anniversary of the establishment of the Psychiatry Department of the Hiroshima University School of Medicine in Hiroshima, Japan. Dr. Su presented a lecture entitled "Drug Action Via Sigma-1 Receptors: New Mechanism for Cognitive Enhancement and Calcium Signaling".

[Office of the Director][Report Index][Next Report Section]

Archive Home | Accessibility | Privacy | FOIA (NIH) | Current NIDA Home Page

National Institute on Drug Abuse

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

February, 2000

Meetings/Conferences

NIDA's DTR&D sponsored a Symposium on **HPA Axis in Psychiatric Disorders** in September 1999, devoted to review of the role of HPA axis in different psychiatric disorders, including drug dependence. The reports presented showed that refractory cocaine addicts are characterized by depressed HPA axis function. Likewise, there is a cluster of psychiatric disorders, which are highly comorbid with cocaine dependence (ASP, PTSD, ADHD, atypical depression), which are also characterized by a hypofunctional HPA axis. Blunted HPA axis and stress response may represent a biological factor contributing to greater vulnerability for drug dependence or might be a biological marker of refractory stimulant dependence. These findings will be summarized in a NIDA report on stress and drug dependence.

A NIDA-sponsored symposium entitled **"Early Environmental Stress and Biological Vulnerability to Drug Abuse,"** was held at the NeuroScience Center on September 9, 1999. The purpose of the symposium was to stimulate new research that will investigate how stress may biologically change an individual's vulnerability to abuse drugs.

On September 29-30, 1999, Dr. Walter Royal, visiting Neurologist from the Johns Hopkins University School of Medicine, and Dr. Jag H. Khalsa of the Center on AIDS and Other Medical Consequences of Drug Abuse (CAMCODA), NIDA/NIH, planned, organized and conducted a workshop entitled **"Metabolic Disorders in the Pathogenesis of Nervous System Damage in HIV-Infected Drug Users".** A group of outstanding clinician scientists (neurologists, neuropathologists, nutritionist, and others) presented current data on and discussed the role of neuroendocrines, micronutrients, vitamins/hormones in the pathogenesis of metabolic disorders in the CNS of HIV-infected drug users and made recommendations for future research. The abstracts and the recommendations will be placed on the NIDA website soon. An executive summary will also appear in a professional journal.

On September 30-October 1, 1999, Lula Beatty chaired a meeting of the **African-American Researchers and Scholars Group (AARSG).** This group advises NIDA on the research needs and concerns of the African-American community.

A NIDA-sponsored symposium entitled **"Brain Mechanisms Underlying Sleep and Drug Abuse"**, was held in Ft. Lauderdale, FL on October 21, 1999 in parallel with a related sleep symposium administered by the American Physiological Society. The purpose of the symposium was to present to the audience of mainly sleep researchers work that demonstrated the similarity between sleep research and drug abuse research.

Dr. Susan Volman, DNRB, chaired a NIDA-sponsored satellite symposium on the opening day of the Neuroscience meeting entitled **"Synaptic Plasticity in Addiction and Other Changes in Behavior."** The purpose of the symposium was to highlight the variety of physiological mechanisms underlying short- and long-term synaptic plasticity that can produce behavioral change under different circumstances and in different parts of the brain. The mechanisms presented included changes in neuronal connectivity, neurotransmitter sensitivity, and ion channel biophysics that alter neural circuit function as a result of development, drug use, learning, and agonistic social interactions.

Rita Liu and Roger Brown, co-chairs of the Neuroscience Work group held a Satellite Symposium at the Society for Neuroscience meeting in Miami Beach, Florida entitled **"NIDA Neuroscience: Current Status and Future**

Directions". The event was held on the evening of October 23, 1999 and consisted of a presentation by a representative of every major division at NIDA. The idea was to inform young investigators of the scope of NIDA activities and the participants of the meeting did a fine job in relating their Institute activities to some aspect of neuroscience and the grant process.

A satellite symposium chaired by Jonathan Pollock, entitled, **"Model Genetic Organisms for the Study of the Nervous System and Behavior"** was held at the Annual Meeting of the Society for Neuroscience in Miami Beach on October 27, 1999. The purpose of this satellite symposium was to discuss new developments and opportunities for the analysis of the nervous system and behavior using the powerful tools of fly, worm and zebrafish genetics which may provide insight into psychiatric disorders and addiction.

Drs. Minda Lynch, DNBR/BSRB, Joe Frascella, DTR&D, Lucinda Miner, OSPC/SPB, and Lynda Erinoff, DESPR/CRB, organized a satellite symposium at the Society for Neuroscience annual meeting, Miami Beach, October 27, 1999. The workshop, entitled **"Career Pathways in Behavioral Neuroscience" was one in a series of events on "Early Career Pathways: Opportunities for Behavioral Researchers,"** was hosted by the Behavioral Science Working Group during 1999. NIDA grantees Dr. Robert L. Balster and Dr. Lisa Gold delivered presentations on "mentoring and being mentored" in drug abuse research. Dr. Miner discussed the NIDA mission and mechanisms for support of research and career development. Twenty poster presentations were included from junior level NIDA supported researchers who have recruited sources of funding from pre- or post-doctoral awards, the B/START mechanism, FIRST awards or career development programs (the K mechanism). The event was well attended and many new contacts were made with young researchers interested in behavioral science.

Dr. Dave Thomas, BNRB, and Dr. Rob Caudle, University of Florida co-chaired a symposium entitled **"Exciting New Advances in Pain Research and Treatment Using Receptor Internalization Technologies"** held on October 28, 1999 in Miami at the annual Meeting of the Society for Neuroscience. There was a press conference related to this meeting held on October 27, 1999. A recent report was also published on this topic by NIDA-grantee Patrick Mantyh and colleagues (Nichols, M.L., Allen, B.J. Rogers, S.D., et al., Transmission of Chronic Nociception by Spinal Neurons Expressing the Substance P Receptor, Science, (286), pp. 1558-1561, 1999.)

At the **1999 Annual Meeting of the Society for Neuroscience** held in Miami, NIDA introduced its Neuroscience at NIDA informational diskette. This web-linked 3.5" floppy diskette contained extensive information on the neuroscience program at NIDA, including contacts, program announcements and an application form. One thousand diskettes were distributed at the meeting.

NIDA held a Town Meeting in Seattle, Washington, entitled **"Understanding Drug Abuse and Addiction: Myths versus Reality"** on November 10, 1999. NIDA Director Dr. Alan I. Leshner and NIDA researchers addressed dissemination of results of NIDA-supported research and demonstrated how these results can be used to deal with problems of drug abuse and addiction at the state and community levels.

On November 15, 1999, NIDA's Special Populations Office held a meeting of the **Historically Black Colleges and Universities (HBCU) Cooperative Agreement Program.** Representatives from the four participating schools, namely North Carolina Central, Florida A & M, Howard and Morgan, met with NIDA staff (Arnold Mills, Leslie Cooper, Pushpa Thadani, Cathy Mills, Daisey Parker) from the Division of Epidemiology, Services, and Prevention Research, the Division of Treatment Research and Development, the Grants Management Branch and the Special Populations Office to discuss program progress and Phase II plans.

On December 2, 1999, NIDA and constituent organizations Join Together, National Families in Action, Community Anti-Drug Coalitions of America and the American Academy of Child and Adolescent Psychiatry launched a "National Research and Education Initiative About Club Drugs". Among other activities, a scientific meeting on **Club Drugs: Raves, Risks, and Research,** was held for experts to discuss current research on these drugs.

On December 2-3, 1999, Ana Anders, Senior Advisor on Special Populations, Special Populations Office, chaired the first meeting of **NIDA's Asian and Pacific Islander (API) workgroup** in Bethesda, Maryland. The group's main task is to inform NIDA's Director, Dr. Alan Leshner, on issues concerning drug abuse in the API population: research gaps, information needs in the community, and research training.

NIDA hosted its **Sixth Annual Constituent Conference** titled, **"Putting Research to Actual Use"** at the Westfields Marriott in Chantilly, Virginia on December 5-6, 1999. NIDA Director, Dr. Alan Leshner presented the "NIDA Report Card," highlighting NIDA's past-year achievements, research findings, and specific actions taken by the Institute in response to constituent group recommendations. Dr. David Rosenbloom, Director of Join Together facilitated a group discussion among the participants regarding past-year successes in using research. Mr. Jeffrey Blodgett, Coordinator of The Alliance Project talked to participants about mobilizing the field toward action and efforts being made by The Project to serve as a focal point of coordination and resource to organizations and activists in the

field. The meeting closed with a discussion facilitated by Dr. Leshner on the future directions for drug addiction research, and constituent representatives provided feedback on NIDA's Strategic Plan.

The first **Retreat of the Transdisciplinary Tobacco Use Research Centers** was held at the Lansdowne Resort in Virginia, December 16-17, 1999. This was the first opportunity for the seven Center awardees to interact with each other and with NIH staff and The Robert Wood Johnson Foundation (RWJF) to plan collaborative activities.

The **NIDA CTN Kick Off Meeting** was held at the Neuroscience Center on November 3-4, 1999. All of the Principle Investigators, co- Principle Investigators and the Directors from the community-based treatment programs from the five awardees were invited to participate. Dr. Leshner provided an overview, vision, mission and objectives for the network. Dr. Tai, Director for NIDA's CTN office led an indepth discussion on the operational infrastructure and management plan for the Network. Dr. Vocci, Director of NIDA's Division of Treatment Research and Development presented NIDA's previous experience on multi-site medications trials. Mr. Gasparis from NIH OPRR presented NIH's human subject protection regulatory issues, Dr. Lawrance Friedman from NHBLI spoke on the new NIH guidelines on Data Safety Monitoring Board responsibilities. The first Steering Committee meeting of the CTN followed.

Mr. Richard A. Millstein, Deputy Director, NIDA, spoke at the African-American Researchers and Scholars Group meeting in Washington, DC on the Clinical Trials Network, October 1, 1999.

Mr. Richard A. Millstein, Deputy Director, NIDA, spoke on the latest research initiatives of NIDA at the Annual Fall Conference on Prevention and Treatment of the Louisiana Department of Addictions, Baton Rouge, LA on November 3, 1999.

Mr. Richard A. Millstein, Deputy Director, NIDA, met with the HBCU Recruited Scientist Cooperative Agreement University P.I.s in Rockville, MD on November 15, 1999.

Mr. Richard A. Millstein, Deputy Director, NIDA, spoke at NIDA's first Asian Pacific Islander Workgroup meeting in Rockville, MD, December 3, 1999.

Mr. Richard A. Millstein, Deputy Director, NIDA, briefed the Secretary of HHS on the findings of the 1999 Monitoring the Future Study in Washington, DC on December 9, 1999. The results were announced at a press conference by the Secretary, ONDCP Director Barry McCaffrey, NIDA Director Dr. Alan Leshner, and MTF P.I. Dr. Lloyd Johnston on December 19, 1999.

Mr. Richard A. Millstein, Deputy Director, NIDA, met with Dr. Christopher Ringwalt, Chair, Alcohol, Tobacco and Other Drugs Section of the American Public Health Association, Dr. William Butynski of the section and Ms. Donna Crane, APHA Government Liaison, Rockville, MD on December 10, 1999.

Dr. Timothy P. Condon, Associate Director, NIDA, and Director, Office of Science Policy and Communications, participated in the "Day of Dialogue Workshop" group discussion with the National Health Museum and the Dana Foundation on September 23, 1999 in New York, NY.

Dr. Timothy P. Condon made a keynote presentation, "Addiction is a Brain Disease:" Implications for Research and Practice" at the American Academy of Child and Adolescent Psychiatry 46th Annual Meeting, October 23, 1999 in Chicago, IL.

Dr. Timothy P. Condon presented for NIDA/EIC Outreach staff "From Lab to Lens", Drug & Youth: Tragedies & Truth-The Sequel on November 8, 1999 in Los Angeles, CA.

Dr. Timothy P. Condon made a keynote presentation for Mayor Menino's Alcohol and Drug Forum, A Community Dialogue: Principles of Effective Treatment from Research to Practice, November 19, 1999 in Boston, MA.

Dr. Timothy P. Condon made a keynote presentation "Science Replacing Ideology" for the Alcoholism and Substance Abuse Providers of New York 3rd Annual Statewide Conference November 15, 1999 in Bolton Landing, NY. In addition, Dr. Jack Stein, Deputy Director, OSPC, facilitated a research to practice track at this conference featuring numerous NIDA grantees.

Dr. Timothy P. Condon conducted a workshop on "Methamphetamine and other Emerging Drug Epidemics for the Community Anti-Drug Coalitions of America, National Leadership Forum X, Celebrating Our Past, Present and Future on December 3, 1999 in Washington, DC. Dr. Jack Stein, conducted a workshop on "The Principles of Drug Addiction Treatment" at this conference.

Dr. Timothy P. Condon participated in the PRISM 2000 Awards Nomination Review Committee held January 22-23, 2000 in Burbank, CA.

Drs. Timothy P. Condon and Jack Stein facilitated several sessions at NIDA's 6th Annual Constituent Conference held December 5-6, 1999 in Chantilly, VA.

Dr. Jack Stein, OSPC, presented a workshop, "Understanding Drug Abuse and Addiction" at the Virginia Commonwealth Community Corrections Conference, November 4 in Williamsburg, VA.

Dr. Jack Stein, OSPC, facilitated a meeting on "Research to Practice" co-sponsored by NIDA and the National Association of State Alcohol and Drug Abuse Directors (NASADAD), held on November 9, 1999 in Seattle, Washington, prior to a NIDA Town Meeting on November 10, 1999 in Seattle.

On October 9-11, 1999, Public Information and Liaison Branch Chief Beverly Jackson served as a member of the Board of Directors for the Partnership for Media Education in El Paso, Texas. This session explored leadership in media education and the vision for the future of media educators in the United States.

On November 7-11, 1999, Technical Writer/Editor David Anderson, Public Information and Liaison Branch, attended the American Public Health Association Conference in Chicago. He met with members of APHA alcohol, tobacco, and other drug special interest groups.

NIDA staff from the Center on AIDS and Other Medical Consequences of Drug Abuse (CAMCODA), participated in the National AIDS Minority Council's 1999 US AIDS Conference in Denver, Colorado, on November 5-8, 1999. Dr. Henry (Skip) Francis, Director, CAMCODA and Dr. Jag H. Khalsa planned, organized and conducted a seminar on: Health Care/Primary Care Access & Utilization by HIV-infected Drug Abusing High-Risk Minority Populations. A group of clinicians/scientists discussed the epidemiology of drug abuse and HIV infection; issues of access and utilization of primary care including the national and international perspectives, adherence and compliance to treatment regimens and interventions applicable to at-risk and minority populations. The abstracts will be placed on the NIDA website and a brief executive summary will be published in a professional journal.

On November 3-4, 1999, Lula Beatty, participated in a conference on "Ethnic Drinking on College Campuses" sponsored by the Center for Substance Abuse Prevention in Bethesda, MD.

On September 28, 1999, Lula Beatty presented a session on drug abuse research and research careers to members in an undergraduate health careers society at the University of Maryland, College Park.

On September 20, 1999, Lula Beatty presented a session on drug abuse research opportunities for HBCUs as part of the Federal government's HBCU Week activities in Washington, DC.

In October 1999, Lula Beatty served as a reviewer for proposals submitted to Division 45 (Ethnic and Minority Affairs) for presentation at the 2000 American Psychological Association's convention.

In October 1999, Lula Beatty served as a reviewer for proposals submitted for presentation at the Head Start Research Conference.

On December 9-10, 1999, as a representative of the Special Populations Office, Arnold Mills, chaired a technical assistance workshop for faculty and staff of Historically Black Colleges and Universities (HBCUs) in Bethesda, Maryland. This workshop was designed to increase participants' knowledge of research application preparation, encourage participants to work independently while utilizing resources and increase participants' knowledge about NIDA staff, research programs and funding mechanisms available to faculty and staff from HBCUs.

Dr. Cora Lee Wetherington moderated the "Focus on Women and Drug Abuse Forum" at the annual conference of the Alcoholism and Substance Abuse Providers of New York State, Lake George, NY, November 14-17, 1999. In the forum, she gave a talk on women, gender, and drug abuse.

Dr. Jaylan Turkkan gave several tobacco use-related presentations. The first, given on November 8, 1999, was a Society for Research on Nicotine and Tobacco meeting co-hosted by the CDC, NIDA, NCI and RWJF entitled "Meeting on Methodology and Outcome Measures for Tobacco Use Cessation." The second, given on December 2, 1999, was a presentation of NIDA's tobacco use research portfolio to the Health Subcommittee of the United Kingdom's House of Parliament.

Dr. Frank Vocci presented the Plenary lecture, "Medications in the Pipeline" at the California Society of Addiction Medicine Meeting at Marina del Ray, California, on October 7, 1999.

Dr. Frank Vocci presented an overview on "Ibogaine" at the California Society of Addiction Medicine Meeting at Marina del Ray, California, October 9, 1999.

Dr. Frank Vocci presented Grand Rounds at the UCLA, Department of Psychiatry, California, November 2, 1999. The title of his presentation was: "Approaches to the Development of Medications for Cocaine Dependence: How Science Informs the Process."

Dr. Frank Vocci gave a presentation, "NIDA's Role in the Development of Ibogaine" at the New York University Conference on Ibogaine, November 5-6, 1999.

Dr. Frank Vocci presented a plenary lecture, "New Medications Development and Treatment" at the Town Meeting: Understanding Drug Abuse & Addiction Myths vs. Reality in Seattle, Washington, November 10, 1999. Dr. Celeste Napier of Loyola University of Chicago was a co-presenter in this session. Her presentation was titled, "Brain Targets of Drugs of Abuse."

Dr. Frank Vocci, Director of DTR&D, and Dr. Andrew Saxon of the Seattle VA Medical Center presented at a workshop "Pharmacotherapies/New Addiction Treatment Medications" at the Town Meeting: Understanding Drug Abuse & Addition Myths vs. Reality in Seattle, Washington, November 10, 1999.

Dr. Frank Vocci presented a lecture, " Medications Development in Cocaine Dependence: Role of Imaging Technologies in the Development Process" at an ACNP symposium, The Emerging Role of Imaging in CNS Drug Development, Acapulco, Mexico, December 15, 1999.

On November 9, 1999, Lisa Onken, Ph.D., DTR&D, presented an overview of NIDA's program of research on behavioral treatment in Seattle, Washington, at the meeting, "Bridging the Gap between Research Policy, and Practice," a meeting co-sponsored by NIDA and NASADAD.

On November 9, 1999, Lisa Onken, Ph.D. gave a presentation on NIDA's Behavioral Therapies Development Program to Dr. G. Alan Marlatt and his research team at the Addictive Behavior Research Center at the University of Washington in Seattle, Washington.

On November 5, 1999, Dorynne Czechowicz, M.D., DTR&D, chaired a symposium on Adolescent Substance Abuse at the American Society of Addiction Medicine State-of-the-Art meeting in Washington, D.C.

On June 18, 1999, Dorynne Czechowicz, M.D. participated in a planning meeting for the "Substance Abuse Regional Training Project" at the Office of Minority Health in Rockville, Maryland.

Drs. Steven Grant and Joseph Frascella, DTR&D, represented NIDA at the dedication of the Sackler Institute for Developmental Psychobiology, and they also attended a one-day symposium on pediatric neuroimaging held in conjunction with the dedication at the Weill Medical College of Cornell University, New York, New York, October 8-10, 1999.

Dr. Steven Grant represented NIDA at the annual meeting of the Psychonomic Society in Los Angeles, November 19-21, 1999.

Dr. Nora Chiang, DTR&D, presented the NIH Small Business funding programs (SBIR and STTR) at the annual meeting of the American Association of Pharmaceutical Scientists, November 14-18, 1999 in New Orleans, LA.

Dr. Deborah Leiderman, DTR&D, gave a presentation on Trial Design and Outcome Measures in Trials for Cocaine Dependence at a joint CPDD/NIDA/FDA meeting on Outcome Measures in Substance Abuse and Dependence, April 1999. Dr. Leiderman also co-chaired the workgroup on cocaine trial outcomes that ultimately resulted in the development of a position paper.

Dr. Meyer Glantz, DESPR, presented a paper entitled "Pathways to Drug Abuse: Predisposing and Protective Factors" to the Community Anti-Drug Coalitions (CADCA) National Leadership Forum X, Washington, D.C., December 1999. The presentation reviewed the research literature and discussed the practical prevention and treatment implications of research on the origins of drug abuse.

Dr. Elizabeth Robertson, DESPR, presented a paper at the12th Annual National Research Conference Prevention Network of the National Prevention Network in Buffalo New York on September 14, 1999. Her presentation was titled "New Directions in Prevention Research" and highlighted the need to develop greater understanding of what makes efficacious prevention strategies successful, for whom and under what conditions.

On December 9, 1999, Ms. Susan David gave a presentation at the 1999 NIH Public Education Forum on Evaluating Mass Media Campaigns. Ms. David presented seven basic questions to be considered in designing an evaluation, and used the NIDA evaluation as an example of how it can be done. Participants included 150 public information staff from NIDA and other Federal agencies.

Dr. Elizabeth Robertson participated in the "Implementation Research: Critical Issues for Future Practice meeting" at Pennsylvania State University on October 10-11, 1999. Recommendations for implementing school-based prevention programming were developed.

As part of her responsibilities on the PHS/CDC/SAMHSA Alcohol Coordinating Team, Dr. Elizabeth Robertson developed a schema for classifying interventions that will be used in the forthcoming chapter reviewing alcohol prevention programs and strategies.

Dr. Bennett Fletcher, Chief, SRB, DESPR, made a presentation at a NIDA-NASADAD-sponsored meeting in Seattle, November 9, 1999.

Dr. Jerry Flanzer, SRB, DESPR, was a keynote speaker (Substance Abuse Treatment and Services Research within ASFA (Adoption and Safe Families Act) Timelines) and workshop leader at the Third National Meeting of States: Sharing Best Practices for Safety, Permanency and Child Well-Being held September 27-28, 1999 in Key Biscayne, Florida. This is a conference led by the National Resource Center for Family Practice targeted at the chief administrators/directors of state child welfare and child protection programs and departments across the nation.

William J. Bukoski, Ph.D., DESPR, represented NIDA at the meeting of the Steering Group/Advisory Committee for the Maryland-ONDCP Partnership. Dr. Bukoski serves as NIDA's representative to the State of Maryland's Youth Drug Use Working Group. The meeting was held at ONDCP, Washington, D.C. The purpose of the meeting was to present and discuss recommendations for action submitted by the State of Maryland's Juvenile Offender, Adult Offender, and Youth Drug Use Working Groups. The meeting was co-chaired by John Carnevale, ONDCP, and Adam Gelb, Lt. Governor's Office, State of Maryland.

In October 1999, at the first meeting of the newly created Cognitive Development Society, Dr. Teri Levitin, Director, OEPR, joined Dr. Herb Weingartner from the NIDA Behavioral Sciences Research Branch to present NIDA's program on cognition. They were on a panel with several other NIH and foundation representatives interested in supporting cognitive development research.

Drs. William Grace, Deputy Director, OEPR, and Teresa Levitin, Director, OEPR, presented a poster and information session at the Society of Research Administrators in Denver, CO on October 18-19, 1999. The session, titled "Enhancing Faculty Involvement in NIH Grant Review," addressed ways in which university and sponsored projects officials could facilitate scientists' involvement in peer review.

Mr. Richard Harrison, Chief, Contracts Review Branch, participated in the annual conference of the American Indian Science and Engineering Society, which was held in Minneapolis in November 1999. He participated in recruitment activities and in a workshop on NIH opportunities for employment and funding.

The OEPR and the Neuroscience Consortium Workgroup, NeuroAIDS subcommittee, co-chaired by Drs. Rita Liu and Lynda Erinoff, held a workshop on November 1, 1999 at the Neuroscience Center on "Applications of Animal Models of NeuroAIDS to Drug Abuse Research." SIV/primate, FIV/feline, SCID, and leukocyte models were discussed.

Dr. David A. Gorelick, IRP, gave an invited presentation on "Cocaine Craving and Relapse: Role of Mu Opiate Receptors," at the American Society of Addiction Medicine State of the Art Conference, Washington, D.C., November 4, 1999.

[Office of the Director][Report Index][Next Report Section]

Archive Home | Accessibility | Privacy | FOIA (NIH) | Current NIDA Home Page

National Institute on Drug Abuse

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

February, 2000

Media and Education Activities

Awards

NIDA received three Galaxy Awards from MerComm, Inc, which is affiliated with the International Academy of Communication Arts and Sciences: **NIDA NOTES special anniversary issue** (Volume 14, Number 1) received a finalist award in newsletter copyrighting. The **NIDA artcard series** developed to advertise Infofax and the web site received a bronze award in the miscellaneous promotion category. The **NIDA Goes to School toolbox** received a gold award in the educational program design category.

Press Releases

September 1, 1999 - **Differences in Human Brain Chemistry May Account for Different Responses to Stimulants.** Scientists have discovered a mechanism that appears to account for the different levels of euphoria people experience when taking a stimulant drug, according to this study funded by NIDA and the US Department of Energy. The study, which appeared in the September issue of the *American Journal of Psychiatry,* found that people who have lower levels of dopamine D2 receptors in their brains are more inclined to like the effects of methylphenidate, a mild stimulant, than people who have higher levels of these receptors and who were found to dislike the drug's effects. As a result of this news release, articles appeared in *Substance Abuse Report and ScienceDaily Magazine.*

September 9, 1999 - **NIDA Celebrates 25th Anniversary of Scientific Progress with a Day of Events for Public and Scientific Audiences.** NIDA held a full day of activities, including an evening event for the general public and an afternoon scientific symposium, on September 27, 1999, at the NIH Clinical Center. Dr. Alan I. Leshner, NIDA Director, hosted the commemoration of NIDA's 25 years of leadership in bringing the power of science to bear on drug abuse and addiction.

September 15, 1999 - **Scientists Identify Brain Chemicals Involved in 'Switching On' Cocaine Addiction.** Scientists supported by NIDA identified two chemicals in the brains of mice that appear to play a major role in the addiction process. The study appeared in the September 16, 1999, issue of *Nature.* Researchers found that adding the extra delta-FosB gene caused mice to become more sensitive to the pleasurable effects of cocaine, a change that is thought to play an important role in the development of cocaine craving and addiction. In addition, researchers found that inserting GluR2, a glutamate receptor subunit, into the nucleus accumbens of mice dramatically enhanced sensitivity to cocaine reward. As a result of this news release, articles appeared in *Reuters Health, The Washington Post, and The Chicago Tribune.*

September 28, 1999 - **NIH Institute Launches National Drug Addiction Treatment Clinical Trials Network. Regional Research Centers Will Work with Community Treatment Programs to Test Drug Abuse Treatments.** In an effort to dramatically improve treatment throughout the country, NIDA awarded $55 in grants over five years to establish a clinical trials network that will more rapidly move promising science-based drug addiction treatments into community settings. As a result of this news release, articles appeared in *Lexis-Nexis*

Universe, The Oregonian, Workplace Substance Abuse Advisor, Alcoholism & Drug Abuse Weekly, as well as on *Lexis-Nexis Universe and Washington Fax.*

October 12, 1999 - **Principles of Drug Addiction Treatment: A Research-Based Guide.** NIDA prepared this guide to summarize basic principles that characterize effective drug addiction treatment, to provide answers to frequently raised questions, to describe the types of treatment, and to present examples of scientifically based and tested treatment components. The guide was released in conjunction with an article by NIDA Director Alan Leshner, entitled "Science-Based Views of Drug Addiction and Its Treatment," that appeared in the October 13, 1999 issue of *The Journal of the American Medical Association.* As a result of this news release, articles appeared in *Reuters Health, UPI Science News, The NIH Word on Health,* as well as on *Lexis-Nexis Universe, M2 Presswire and Washington Fax.*

October 18, 1999 - **Federal Institutes and The Robert Wood Johnson Foundation Create Tobacco Use Research Centers.** Seven academic institutions were awarded grants totaling $14.5 million by the National Cancer Institute (NCI) and NIDA to create the Transdisciplinary Tobacco Use Research Centers for studying tobacco use and new ways to combat it and its consequences. The Robert Wood Johnson Foundation committed an additional $14 million over five years to complement NCI's and NIDA's efforts to improve the policy understanding and communications practices of the tobacco research teams. As a result of this news release, articles appeared in *The Los Angeles Times, Wisconsin State Journal Online, Star Tribune, Capital Times,* as well as on WKOW television.

December 2, 1999 - **Club Drugs Take Center Stage in New National Education and Prevention Initiative by NIDA and National Partners.** As part of a national initiative to combat the increasing use of club drugs, NIDA announced at a news conference that it will raise its funding for research about club drugs and what to do about them by 40 percent, bringing the total committed to this important effort to $54 million. In addition, NIDA and four national organizations launched a multi-media public education strategy to alert teens, young adults, parents, educators and others about the dangers of club drugs such as Ecstasy, GHB and Rohypnol, which are often used at all-night "raves" or dance parties and have potentially life-threatening effects. NIDA's partners in this initiative include the American Academy of Child and Adolescent Psychiatry, the Community Anti-Drug Coalitions of America, Join Together and National Families in Action. This news conference generated broad coverage that included stories on every major television network-CBS, NBC, MSNBC, ABC, and CNN. In addition, the Associated Press article about the news conference appeared in newspapers across the country. Articles also appeared in *USA Today, U.S. News & World Report,* and other publications.

December 17, 1999 - **1999 Monitoring the Future Survey.** Health and Human Services Secretary Donna E. Shalala and Barry McCaffrey, director of the Office of National Drug Control Policy, announced the results of the 25th annual Monitoring the Future Study on illicit drug use among teens at the HHS Headquarters in Washington, DC. The Monitoring the Future Survey, conducted by the University of Michigan's Institute for Social Research and funded by NIDA, has tracked 12th graders illicit drug use and attitudes towards drugs since 1975. In 1991, 8th and 10th graders were added to the study. The 1999 study surveyed more than 45,000 students in 433 schools across the nation about their lifetime use, past year use, past month use, daily use of drugs, alcohol, cigarettes, and smokeless tobacco. As a result of this news release, articles appeared in *The New York Times, The Washington Post, The Washington Times, The Atlanta Constitution, St. Louis Post-Dispatch, Reuters Health, USA Today, Seattle Post-Intelligencer, and The Los Angeles Times.* Stories also aired on CBS, CNN, MSNBC, and ABC News.

December 17, 1999 - **Nicotine Vaccine Shows Promise for Combating Tobacco Addiction.** Researchers funded in part by NIDA have found that a nicotine vaccine may be an effective method for preventing and treating tobacco addiction. According to a paper published in the December 17 issue of *Pharmacology, Biochemistry and Behavior,* the scientists associated with the Minneapolis Medical Research Foundation and Hennepin County Medical Center, the University of Houston-Clear Lake, and Nabi, a pharmaceutical firm based in Boca Raton, Florida, have developed a nicotine vaccine consisting of a nicotine derivative attached to a large protein. The press release announcing this finding received broad coverage, including an interview with NIDA Director Alan Leshner on the CBS Evening News. In addition, articles about the vaccine appeared in the *Boston Globe, Minneapolis Star Tribune,* and other newspapers.

Opinion Pieces/Letters

September 5, 1999, *Boston Globe*- Commentary by Alan I. Leshner - "The Sense in Saving Drug Addicts."

October 13, 1999, *The Journal of the American Medical Association*- Commentary by Alan I. Leshner - "Science-Based Views of Drug Addiction and Its Treatment."

November 2, 1999, *Seattle Post-Intelligencer*- Commentary by Alan I. Leshner - "Harmful Drugs on Rise in Seattle."

November 1999, *THE FUTURIST*- Commentary by Alan I. Leshner - "We Can Conquer Drug Addiction."

December 1, 1999, *Letter to Dear Abby* from Alan I. Leshner - "'Club Drugs' not harmless as portrayed." (Dear Abby is published by Universal Press Syndicate in newspapers across the country.)

NIDA Exhibits Program

The following are meetings where NIDA exhibited its publications and program announcements over the past several months:

September 27, 1999	NIDA 25th Anniversary Symposium
October 7-9, 1999	National Association of Social Workers
October 7-11, 1999	Society for Advancement of Chicanos and Native Americans in Science
October 9-13, 1999	American Academy of Pediatrics
October 19-23, 1999	American Society of Human Genetics
October 19-24, 1999	American Academy of Child and Adolescent Psychiatry
October 23-28, 1999	Society for Neuroscience
October 27-30, 1999	American Psychiatric Nurses Association
October 30-November 2, 1999	Hispanic Association of Colleges and Universities
November 4-6, 1999	Association of Medical Education and Research in Substance Abuse
November 5-7, 1999	AIDS Meeting
November 10, 1999	NIDA Town Meeting-Seattle
November 7-11, 1999	NAmerican Public Health Association
November 10-13, 1999	National Minority Research Symposium & Minority Access to Research Careers
November 11-14, 1999	Association for Advancement of Behavior Therapy
November 14-17, 1999	Alcoholism & Substance Abuse Providers of New York State
November 18-21, 1999	American Indian Science & Engineering Society
December 1-4, 1999	Community Anti-Drug Coalitions of America
December 2-5, 1999	American Academy of Addiction Psychiatry
December 11-15, 1999	American Society for Cell Biology

[Office of the Director][Report Index][Next Report Section]

Archive Home | Accessibility | Privacy | FOIA (NIH) | Current NIDA Home Page

The National Institute on Drug Abuse (NIDA) is part of the National Institutes of Health

National Institute on Drug Abuse

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

February, 2000

Planned Meetings

A final meeting of grantees funded under the **NIH Consortium on Domestic Violence** administered by NIDA (Dr. Coryl Jones, ERB/DESPR) will be held in April 2000, in Washington, DC, to discuss progress, findings, and problems in this type of research. Other investigators with studies on violence against women and within the family funded by participating Institutes and agencies, including the National Institute of Justice and the Children's Bureau, will also be invited. Following this meeting, a national conference on violence against women and within the family is planned to provide a broader forum for findings resulting from this NIH Consortium.

Dr. William J. Bukoski, DESPR, serves as NIDA's representative to the Washington Area Council of Governments (COG)---Drug Prevention and Education Committee and is a member of the steering committee that will help plan COG's drug prevention conference scheduled for May 1, 2000. On July 28, 1999, the Drug Prevention Education Committee met to update members on forthcoming prevention activities sponsored by local jurisdictions, to discuss proposed committee activities, and to begin planning the COG drug abuse prevention conference. The theme of the conference is **"Bridging Prevention Science and Practice,"** and will feature local and national science-based drug prevention strategies. Dr. Alan Leshner will provide the keynote address.

A conference entitled **"Assessing the Impact of Childhood Interventions on Subsequent Drug Abuse"** (Dr. Meyer Glantz, OD/DESPR, and Dr. Naimah Weinberg, ERB/DESPR, co-chairpersons), will be held in Washington, D.C., at Hotel Washington on May 23-24, 2000. NIDA and NIMH are co-sponsoring this meeting to assess the impact of mental health treatments for childhood psychopathologies on subsequent risk for drug abuse to assist drug and mental health investigators develop this important research area. More details will soon be available at http://www.nida.nih.gov/ICAW/ICAW.html.

The Behavioral Science Working Group is developing a thematic track and a series of events focusing on vulnerability to drug abuse for the next meeting of the American Psychological Association (APA, August 2000). The track, entitled **"Advances in Understanding Vulnerability to Drug Abuse"** is a followup to NIDA's highly successful Conference on Drug Abuse (CODA) that was held at APA in 1996. Planned are a pre-conference satellite day (on Thursday August 3rd) focused on young investigator careers in drug abuse research, followed by invited speakers during the APA meeting on subsequent days, including an invited address by Dr. Leshner. Several student travel awards, co-sponsored by the Science Directorate of the APA, are also planned as part of these activities.

[Office of the Director][Report Index][Next Report Section]

Archive Home | Accessibility | Privacy | FOIA (NIH) | Current NIDA Home Page

National Institute on Drug Abuse

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

February, 2000

Publications

National Survey Results on Drug Use from the Monitoring the Future Study, 1975-1998.
Volume I: Secondary School Students (NIH Pub. No 99-4660)
Volume II: College Students and Young Adults (NIH Pub. No 99-4661)
These two publications (both printed in September 1999) report the cumulative findings of the NIDA-supported Monitoring the Future study which examines the prevalence of drug use among American secondary students (i.e. 8th, 10th, and 12th grades), college students, and young adults.

Epidemiologic Trends in Drug Abuse: Community Epidemiology Work Group,
Vol. I, June 1999
NIH Pub. No. 00-4529
This publication provides more detailed descriptions of drug abuse patterns, trends, and consequences reported in the Advanced Report. The report provides an ongoing assessment of epidemiology of drug abuse in major metropolitan areas of the United States with the purpose of keeping both public and private sector policy makers and researchers informed with current and accurate data.

Epidemiologic Trends in Drug Abuse: Community Epidemiology Work Group,
Volume II: International Epidemiology Work Group on Drug Abuse, June 1999
NIH Pub. No. 00-4530
This publication includes papers from the International Epidemiology Work Group (IEWG) that is a network of drug abuse researchers from various countries, regions, and international organizations. It includes efforts to establish a global drug abuse surveillance network.

NIDA Community Drug Alert Bulletin-Club Drugs
NIH Pub. No. 00-4723
NCADI - PHD827
The Community Drug Alert Bulletin on Club Drugs provides a synopsis of NIDA's research knowledge on club drugs and refers individuals to additional reliable sources of information.

NIDA NOTES

NIDA NOTES Vol. 4, Issue 3
NCADI - NN0038

This issue's lead article and Director's Column deal with the subtle but significant effects of prenatal cocaine exposure. The Atlanta Town Meeting, NIDA's biggest so far, is covered. Another article looks at how a NIDA-supported science education project in a California high school is sparking student interest in science in general and drug abuse research. The Tearoff offers information in brief on cocaine abuse and treatment.

NIDA NOTES, Vol. 4, Issue 4
NCADI - NN0039

The lead story in this issue describes how twin studies provide valuable information on the interrelationship between genetic and environmental risk factors for drug abuse. The Director's Column examines how comorbid mental health problems complicate drug abuse treatment. A related article looks at the relationships between attention-deficit/hyperactivity disorder and drug abuse. The effects of "ecstasy" on the brain and memory are reviewed and the Tearoff provides a primer on the drug. NIDA's new Teen Tobacco Addiction Treatment Research Clinic is highlighted in this issue as well.

Drug Abuse: Origins and Interventions. Meyer Glantz and Christine Hartel (Eds.). Washington, D.C., American Psychological Association Press, 1999. Based on a NIDA-APA sponsored conference, this book includes 14 chapters by leading drug abuse researchers on new findings in a range of different drug abuse fields and their implications and three chapters reviewing and synthesizing the research on the origins, prevention, and treatment of drug abuse.

Resilience and Development: Positive Life Adaptations. Meyer Glantz and Jeannette Johnson (Eds.). New York: Kluwer Academic/Plenum Press, 1999. Based on a multi-institute sponsored conference, this book presents the latest findings, concepts and applications of research on resilience through chapters written by the leading experts in the field. The book is the 3rd volume in the Interdisciplinary Series entitled: Longitudinal Research in the Social and Behavioral Sciences.

The Origins of Drug Abuse: Mapping the Paths. M. Glantz, N. Weinberg, L. Miner and J. Colliver. In M. Glantz and C. Hartel (Eds.). Drug Abuse: Origins and Interventions. Washington, D.C., American Psychological Association Press, 1999. This chapter reviews the research literature on the origins and development of drug abuse.

The Treatment of Drug Abuse: Changing the Paths. C. Hartel and M. Glantz. In M. Glantz and C. Hartel (Eds.). Drug Abuse: Origins and Interventions. Washington, D.C., American Psychological Association Press, 1999. This chapter reviews the research literature on the treatment of drug abuse.

Analysis and Reconceptualization of Resilience. M. Glantz and Z. Sloboda. In M. Glantz & J. Johnson (Eds.), Resilience and Development: Positive Life Adaptations. New York: Plenum Press 1999. This chapter analyses the concept of resilience and proposes an alternative approach to the use of the concept.

Frontline Surveillance: the Community Epidemiology Work Group on Drug Abuse. Zili Sloboda and Nicholas Kozel. In M. Glantz and C. Hartel (Eds.). Drug Abuse: Origins and Interventions. Washington, D.C., American Psychological Association Press, 1999. This chapter discusses the history and function of the CEWG with a discussion of the unique characteristics that make its work important.

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[Office of the Director][Report Index][Next Report Section]

Archive Home | Accessibility | Privacy | FOIA (NIH) | Current NIDA Home Page

National Institute on Drug Abuse

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

February, 2000

Staff Highlights

Awards

NIDA Director's Awards (Individual)

Dr. Jonathan Pollock, DNBR, was recognized for his important contributions to the development of NIDA and NIH-wide programs especially in the area of genetics as well as molecular biology, and developmental neuroscience.

Ms. Elizabeth Lambert, DESPR, was recognized for her outstanding contributions in support of the programmatic, scientific, and administrative activities of the Community Research Branch.

Ms. Ann Hutzler, DESPR, was recognized for her significant role in enhancing the quality of worklife and advancing understanding and collaboration among Division staff.

Dr. Eric Moolchan, IRP, was recognized for his innovation and leadership in the adolescent smoking cessation protocol which created an opportunity for NIDA to focus clinical treatment research on the under served adolescent population.

Dr. Roy Wise, IRP, was recognized for his outstanding accomplishments to a series of significant studies of fluctuations of nucleus accumbens dopamine during intravenous self-administration of cocaine, amphetamine and heroin.

Dr. James Terrill, DTR&D, was recognized for his exceptional initiative and leadership in shaping and directing the NIDA Toxicology Program and coordinating it with related chemistry, pharmacokinetic, and clinical efforts within the Division.

Dr. Jane Acri, DTR&D, was recognized for her superb skill and leadership in shaping and directing NIDA's preclinical medication discovery programs.

Ms. Pamela Goodlow, SPO, was recognized for her outstanding management and coordination of the logistics contract which supports the majority of the workshops and meeting sponsored by the Special Populations Office.

Mr. Berhane Yitbarek, IRMB/OPRM, was recognized for his initiative and self-reliance in continuing to provide a high level of technical and administrative ADP support to NIDA staff.

Ms. Donna Tolson and Ms. Traci Pelan, MASB/OPRM, were recognized for their cooperative attitude, reliability and a willingness to help staff accomplish the many varied administrative activities of the Institute.

Dr. Khursheed Asghar, OEPR, was recognized for his significant scientific leadership, resourcefulness and competence in meeting the objectives of NIDA's medications development initiatives.

Dr. Susan Coyle, OEPR, was recognized for her resourcefulness, competence, and innovativeness in the complex reviews of the applications for the Clinical Trials Network.

Ms. Niki Andrews, OSPC, was recognized for her outstanding leadership in managing the diverse and often complex operations of the Office of Science Policy and Communications.

Dr. Cindy Miner, OSPC was recognized for her extraordinary responsibility and dedication to improving and increasing the research training program.

NIDA Director's Awards (Group)

Office of Extramural Program Review Team was recognized for their initiative, competence and great teamwork in contributing to the successful reviews of all applications assigned to OEPR:

Ms. Kimberly Crown
Ms. Camilla Holland
Ms. Monglan Le
Ms. Jacqueline Porter
Ms. Pamela Stokes
Ms. Diana Souder
Ms. Marilyn Thomas
Mr. Randolph Williams

NIDA Move Committee was recognized for their role in NIDA's two-year move project while continuing to carry out the duties of their positions. The outstanding work performed by these individuals resulted in a smooth and highly efficient move.

Stephen R. Gane, OPRM
Suzanne M. Cole, OPRM
Donna Tolson, OPRM
Traci Z. Pelan, OPRM
Pamela L. Oliver, OD
Janice F. Walden, OD
Flair A. Lindsey, SPO
Jacqueline R. Porter, OEPR
Pamela K. Stokes, OEPR
Gloria J. Fox, DTR&D
Joseph Frascella, DTR&D
Joyce A. Williams, DNBR
M. Beth G. Babecki, DNBR
Carol A. Cushing, DTR&D
Dorothy J. Grant, DTR&D
Lajuan B. Beckham, DTR&D
Melanie A. Pickett, DESPR
Ann R. Hutzler, DESPR
Kathy E. Etz, DESPR
James D. Colliver, Jr., DESPR
Elizabeth Cooper, DESPR
Carol A. Cornwell, OPRM
Catherine Mills, OPRM
Dale S. Weiss, OPRM
Joanna D. Mourtzanakis, OPRM
Rosemary C. Pettis, EEO
Carole N. Andrews, OSPC
Monica L. Jones, OSPC
John E. Nagy, OSPC
Terry J. King, OPRM
Gerald S. Brodsky, OPRM
Earle A. Stalfort, Jr., OPRM
Maryann P. Postorino, OPRM
Bridget A. Wells, OPRM
Chanvadey D. Nhim, OPRM
Montrue E. Nelson, OPRM
David C. Jones, OPRM

Joseph O. Reckley, OPRM
Tina Mcdonald-Bennett, OPRM
Frank H. Feustel, OPRM
Marguerite M. Lewis, OPRM
Berhane Yitbarek, OPRM

1999 NIDA EEO Awards

Dr. Hari Singh, DNBR, was recognized for his active and enthusiastic support in assisting the NIH Office of Equal Employment and the Director of the Institutes to promote managing diversity, affirmative action and other OEO actions.

Ms. Pam Oliver, ES/OD, was recognized for her support of the EEO advisory committee. Pam has served on the NIDA equal employment opportunity advisory committee for the past 2 years and was recently elected as chairperson in April 1999.

NIDA Picnic Committee: This award is to recognize the **IRP staff** who worked tirelessly to plan, organize, and host the 3rd annual NIDA picnic.

Mr. Brian Alston
Ms. Cindy Ambriz
Ms. Christie Brannock
Ms. Janis Diven
Mr. Morgan Dubrow
Ms. Lena Eads
Ms. Anne Gupman
Ms. Linda Kazlo
Ms. Erin Manor
Mr. James Mckenzie
Ms. Dorothea Moon
Ms. Mary Pfeiffer
Ms. Mary Jane Robinson

Commissioned Corps Awards

Commendation Medal

Dr. Betty Tai, DTR&D, was recognized for her exceptional contributions in designing and implementing the Strategic Program for Innovative Research on Cocaine Addiction Pharmacotherapy (SPIRCAP).

Achievement Medal

Ms. Leslie Cooper, DESPR, was recognized for contributing significantly to NIDA's goal for increasing the participation of Historically Black Colleges and Universities in drug abuse research.

Dr. Ahmed M. Elkashef, DTR&D, was recognized for organizing The Bronchial Asthma/ Cocaine meeting.

Ms. Janice Carico, IRP, was recognized for chairing the Policy Committee that wrote the NDA/IRP confidentiality policy and continuing commitment to maintaining confidentiality of clinical and research information.

PHS Citation

Dr. Paul J. Na, IRP, was recognized for performing controlled substance audits in an exemplary and highly professional manner.

Crisis Response Service Award

Ms. Janice Carico, IRP, was recognized for participating in the crisis PHS interventions at Fort Dix, New Jersey and at Tinian, Commonwealth of Northern Mariana Islands.

Other Honors/Awards

Dr. Kathy Etz, PRB, DESPR, as a member of the Reporting Committee of the Federal Interagency Forum on Child and Family Statistics Team, received Vice President Gore's Hammer award from the National Partnership for Reinventing Government. The team was recognized for its work on America's Children: Key National Indicators of Well-Being.

Dr. Jerry Flanzer, SRB, DESPR was appointed for a two year term as the Chair of the National Steering Committee of the Alcohol, Tobacco and Drug Section of the National Association for Social Workers.

Dr. Lula Beatty, Chief, Special Populations Office was elected to the Committee on Women in Psychology, American Psychological Association in November 1999. This is one of the governance committees in the Public Interest Directorate.

Dr. Susan Boyd, Clinical Fellow, IRP, won the 1999 Addiction Award for best scholarly paper prepared by a physician fellow in addiction. The award is sponsored by the American Academy of Addiction Psychiatry (AAAP) in collaboration with the American Society of Addiction Medicine and the Association for Medical Education and Research in Substance Abuse. Dr. Boyd received the award and presented her paper ("The relationship between parental history and substance use severity in drug treatment patients") at the annual meeting of AAAP December 2-5, 1999.

Dr. Amy Newman, IRP, was honored by the Japanese Pharmaceutical Society with the 1998 Sato International Memorial Award. She was invited to present a talk entitled "Novel Probes for the Dopamine Transporter" on her research at the 119th Annual Meeting of the Pharmaceutical Society of Japan, in Tokushima in March 1999.

Staff Changes

Brenda Fogel joined OSPC in November 1999 as a Program Analyst. Prior to joining NIDA, Ms. Fogel worked for Naval Surface Warfare Center (formerly David Taylor Model Basin) in the Human Resources office assisting the Human Resources Director and Deputy Director with various human resources projects. Ms. Fogel is responsible for assisting the Deputy Director, OSPC with the day-to-day administrative functions of the Office as well as handling special projects for the OD/OSPC.

Ivan Montoya, M.D. joined NIDA's Division of Treatment Research and Development as a Special Expert on December 6, 1999. Dr. Montoya's work will be primarily with the Clinical Trials Network. Dr. Montoya received his M.D. from the University of Antioquia in Columbia and holds an M.P.H. from Johns Hopkins University. Dr. Montoya was a resident at St. Vincent Hospital, Columbia, and the University of Maryland Hospital, Baltimore. Prior to joining DTR&D he was a visiting fellow at the NIDA IRP, a consultant for WHO, and, most recently, served as Director, Practice Research Network, American Psychiatric Association.

Lanette Palmquist joined OSPC in November 1999 as a Program Analyst and Special Assistant to the Associate Director, NIDA. Prior to joining NIDA, Ms. Palmquist was a Program Analyst in the Office of Science Policy at the National Center for Research Resources, NIH for 8 years. Ms. Palmquist is responsible for assisting the Associate Director with policy analysis and preparing slides and talking points for presentations by the Associate Director.

Rebecca Rasooly, Ph.D., joined NIDA's Division of Neuroscience and Behavioral Research on August 29, 1999. Most recently, before coming to NIDA, Dr. Rasooly was Assistant Professor of Pediatrics at the Johns Hopkins University School of Medicine working as the Assistant Deputy Scientific Director for OMIM, one of the National Library of Medicine's on-line suite of databases describing human genes. Dr. Rasooly received her Ph.D. in genetics from Michigan State University and carried out post-doctoral work at the Albert Einstein College of Medicine.

Carmen Luz Rosa joined NIDA's Division of Treatment Research and Development as a Clinical Trials Specialist on September 12, 1999. Before coming to NIDA Carmen was with the Department of the Navy.

Meg Scofield joined the staff of OSPC's Public Information Liaison Branch in December 1999, as a Program Analyst. Ms. Scofield will work on a variety of communication projects involving writing, editing, working with the media, publication production, and project marketing. Previously, Ms. Scofield was the program coordinator for the clinical director, National Eye Institute. She received her M.A. in writing from Johns Hopkins University.

Tony Simon, Ph.D. joined NIDA's CAMCODA in August 1999 on a Science and Engineering Fellowship from the Society for Research in Child Development /American Association for the Advancement of Science. Dr. Simon is a developmental cognitive neuroscientist who was trained in Britain and has held research and teaching positions at Carnegie Mellon University and Georgia Institute of Technology. He is leading a NIDA initiative toward pediatric

neuroimaging assessments of prenatal and early drug exposure effects on brain and behavioral development.

Keith Van Wagner joined the Science Policy Branch, OSPC in August 1999 and is the new project officer for the NIDA Science Meetings contract. Prior to joining OSPC, Mr. Van Wagner earned his Masters in Public Administration from North Carolina State and participated in the Presidential Management Intern program. Mr. Van Wagner will also participate in legislative and congressional activities.

Emma Williams joined NIDA's Budget Office in September 1999 as a Budget Analyst. Prior to coming to NIDA Ms. Williams was with the National Human Genome Research Institute.

Lucinda Miner, Ph.D. was recently appointed as Deputy Chief, Science Policy Branch, OSPC. Dr. Miner has been with NIDA for approximately 7 years and has been with the Science Policy Branch since late 1996. Dr. Miner also serves as the Deputy Coordinator for NIDA's Research Training program.

Dr. Amy Newman was awarded tenure at NIDA-IRP in March 1999 and was named the Chief of Medicinal Chemistry Section in the newly formed Medications Discovery Branch, shortly thereafter.

Dr. Monique Ernst was appointed as Staff Physician in the Neuroimaging Branch, IRP in October 1999.

Dr. Andrew G. Horti was appointed as Staff Scientist in the Neuroimaging Branch, IRP in November 1999.

Ann Blanken, Deputy Director since 1989 and currently Acting Director, Division of Epidemiology, Services, and Prevention Research, National Institute on Drug Abuse (NIDA) retired from federal service December 31,1999. Joining NIDA as a statistician in 1975, Ms. Blanken was involved in the development and management of national data collection systems and in the monitoring of patterns and trends in drug abuse; she subsequently served in numerous positions of increasing responsibility and note. She has played many important roles in the furthering of NIDA's research programs and worked tirelessly to facilitate and improve the function of the division. It is with sincere appreciation that the Institute and the staff thank Ms. Blanken for her unstinting dedication, her many accomplishments, and her unceasing commitment and caring for the staff and the mission of the Institute.

Mr. Richard A. Millstein, NIDA Deputy Director, is also serving as the Acting Director of NIDA's Division of Epidemiology, Services and Prevention Research, effective January 1, 2000.

[Office of the Director][Report Index][Next Report Section]

Archive Home | Accessibility | Privacy | FOIA (NIH) | Current NIDA Home Page

National Institute on Drug Abuse

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

February, 2000

Grantee Honors

Dr. Harriet de Wit, University of Chicago, was named by the Division of Psychopharmacology and Substance Abuse (28) of the American Psychological Association (APA) as the 1999 recipient of the Solvay Award. This award, sponsored by Solvay Pharmaceuticals, recognizes outstanding basic psychopharmacological research on affective disorders by senior investigators. The award was presented at the 1999 APA meeting in Boston, and consisted of a cash award of $2,500, an original sculpture, and an invitation to address the APA meeting as well as an invitation to address the annual meeting of the Behavioral Pharmacology Society and to contribute a review paper to Psychopharmacology.

Dr. Bonnie Gance-Cleveland of the University of Colorado received the Excellence in Advanced Practice Award from the Society of Pediatric Nurses for her research on school-based health centers for adolescents with addicted parents.

[Office of the Director][Report Index]

Archive Home | Accessibility | Privacy | FOIA (NIH) | Current NIDA Home Page