mazocine) produced a maximum analgesic effect (i.e., 20-sec latency) at both 50° and 55°C. The analgesic actions of these agonists were dose-dependent, time-dependent, prevented by small doses of opioid antagonists, and when administered in combination, the analgesic effects of two agonists were additive. Other drugs (e.g., nalbuphine, buprenorphine) also increased in a dose-related manner latency for tail removal from 50°C water. Although the analgesic effects of these agonists also were prevented by opioid antagonists, these compounds, up to very large doses, failed to produce a full effect with 50°C and in some cases produced no effect with 55° water. Moreover, compounds with partial agonistic actions attenuated partially the analgesic effects of the compounds with full agonistic actions. For example, at 50°C, buprenorphine produced a maximum analgesic response of 70% at a dose of 1.0 mg/kg and less effect at doses larger than 1.0 mg/kg. No analgesia was obtained with any dose of buprenorphine at 55°C; however, the analgesic effects of buprenorphine at 55°C were attenuated by the opioid antagonist quadazocine. No analgesic effects were evident 24 hr after doses of buprenorphine as large as 5.6 mg/kg; however, for up to several weeks after administration of buprenorphine, the analgesic effects of full agonists were antagonized up to doses of drug that decreased markedly respiratory function. The results demonstrate a long-lasting irreversible antagonistic action for buprenorphine in rhesus monkeys and further suggest that, under conditions where significant intrinsic activity is required for a maximum behavioral response, opioid partial agonists attenuate the actions of opioid full agonists. (Supported by USPHS Grant DA 00254.)

ADDICTION TREATMENT: POTENTIAL UTILITY OF AGONIST/ANTAGONISTS. George E. Bigelow. The Johns Hopkins University School of Medicine, Baltimore, MD.

Human subjects were used to assess the pharmacological treatment of opioid drug dependence and the potential role that opioid mixed agonist/antagonists might play in improving the range of efficacy of therapeutic alternatives for this behavioral disorder. The two primary pharmacological treatments that have been developed, approved and marketed at this time for the treatment of opioid (heroin) addiction are methadone and naltrexone. Methadone is an opioid agonist, while naltrexone is an opioid antagonist; the strengths and weaknesses of each of these modalities will be discussed. The more recently developed opioid mixed agonist/antagonists could theoretically offer some novel advantages for the treatment of opioid abuse and dependence. These compounds exert opioid agonist actions under some conditions and opioid antagonist actions under other conditions. To assess their potential utility in addiction treatment requires careful assessment of the conditions under which their agonist versus antagonist actions prevail. Data will be presented from a series of such clinical behavioral pharmacology studies. Both butorphanol and nalbuphine have been found to have little therapeutic potential for addiction treatment because both drugs precipitate an opioid withdrawal syndrome when administered to opioid-dependent subjects. Of the currently available mixed agonist/antagonists, buprenorphine appears to have the greatest potential in addiction treatment. In one clinical therapeutic study with addict subjects, buprenorphine (2 mg sublingually) was compared to the standard current treatment of methadone (30 mg orally) in the outpatient detoxification treatment of addicts and was found to be equiefficacious as assessed by patient retention, withdrawal symptoms and illicit drug use. In a second study, a range of doses of sublingual buprenorphine (2, 4, 8, 16 mg) was assessed with respect to their ability to attenuate the effects of an opioid agonist challenge injection (hydromorphone, 18 mg IM). A buprenorphine dose-related attenuation of hydromorphone effects was observed, with appreciable attenuation occurring with the 4–8 mg doses. We conclude that buprenorphine offers considerable promise for the treatment of opioid addiction since it is acceptable to patients, does not precipitate withdrawal at therapeutic doses, attenuates the effects of opioid agonists for at least 24 hours, and does not itself sustain appreciable physical dependence.

PROLONGED SELF-ADMINISTRATION OF MORPHINE AND ADDICTION LIABILITY IN CLINICAL SETTING. C. Richard Chapman. University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA.

Patient-Controlled Analgesia (PCA) systems are microprocessor-controlled infusion units which permit patients to trigger intravenous boluses of morphine at preset magnitudes and limited frequency. PCA has been successful for postoperative analgesia, but patients only require drug for a few days. Concern remains that cancer patients and others may self-administer morphine long enough to develop tolerance, dependence and, eventually, addiction. This study compared two competing theories and tested their predictions about self-administration of morphine over two weeks using data obtained from patients in a bone marrow transplant unit. The first, Opponent Process Theory, predicts escalating drug use and the development of addictive behavior. Patients' motives are expected to change over time when their behaviors have affective consequences. Patients who initially self-administer morphine for pain relief will progress through stages in which tolerance develops, healing progresses so that pain relief becomes unimportant, and they come to use the drug to avoid the opioid abstinence syndrome. The second approach, Control Theory, applies cybernetic principles and construes the patient using PCA for pain control as an effective self-regulating system. It recognizes that unique circumstances determine what people do when self-regulating and characterizes patients in terms of multiple goals and control loops that are coherently interrelated and hierarchically organized. Data were obtained from patients who had severe treatment-induced oral mucositis pain. Patients ($N=12$) self-administering morphine were compared to controls ($N=14$) who received staff-controlled continuous infusions. Self-administering patients used only 58% as much morphine as controls ($p=0.026$) but achieved similar analgesia, used significantly less drug per hour ($p=0.034$), and terminated drug use approximately three days sooner. The predictions of Opponent Process Theory were not supported, but Control Theory accounted well for the outcomes. The results confirm that self-administration of opioids in a medical setting does not put patients at risk for drug abuse.

EFFECTS OF AGONIST AND ANTAGONIST CHALLENGES IN BUPRENORPHINE-TREATED VOLUNTEERS. Paul J. Fudala, W. Robert Lange, Charles C. Collins and Rolley E. Johnson. National Institute on Drug Abuse Addiction Research Center, Baltimore, MD.

Fourteen heroin-dependent volunteers were stabilized on 8 mg of sublingually administered buprenorphine hydro-

chloride (BUP) in a 30% (v/v) ethanol solution given daily for 16 days. Six hours following BUP administration on days 14, 15 and 16, subjects were randomly assigned to receive a single intravenous (IV) or intramuscular (IM) injection of hydromorphone hydrochloride (HDM), 0, 2 or 4 mg. Using a parallel groups design, subjects were randomly assigned to one of two groups (A or B). Group A continued to receive 8 mg of BUP daily for another 18 days (days 17 through 34); Group B received 8 mg every other day (alternating with placebo) over the same 18-day period. Six hours following BUP administration on days 29 through 34, subjects again received a randomly determined single daily IV or IM injections of HDM, 0, 2 or 4 mg. The last BUP dose was given to each group on day 34, and placebo continued through day 54. Six hours following BUP placebo administration on days 51 through 54, subjects received a randomly determined single daily IV or IM injection of naloxone hydrochloride (NAL), 0, 3, 6 or 12 mg. Physiological and behavioral observations were performed at −1 and −0.5 (preHDM/NAL) as well as 0.5, 1, 2 and 4 hr following HDM or NAL administration. Physiological observations included measurements of supine and standing blood pressure and heart rate, respiratory rate, pupil diameter, and body temperature. Subscales of the Addiction Research Center Inventory, Observer and Subject Drug Effect Questionnaires, and the Withdrawal Symptom Questionnaire were used to rate behavioral signs and symptoms of acute opioid effect and withdrawal.

INVITED ADDRESS

Food Effects on Brain and Behavior
Richard J. Wurtman, Massachusetts Institute of Technology, Cambridge, MA
Chair: *Peter B. Dews,* Harvard Medical School, Boston, MA

SYMPOSIUM

CNS Stimulants, Aggression and Prosocial Behavior: ADD Children and Animals
Chair: *James M. Swanson,* Child Development Center, University of California, Irvine, CA
Discussant: *Markus Kreusi,* National Institute of Mental Health, Bethesda, MD

AMPHETAMINE'S EFFECTS ON THE SOCIAL BEHAVIOR OF GROUP-LIVING MONKEYS. Larry D. Byrd and Euclid O. Smith. Yerkes Regional Primate Research Center, Emory University, Atlanta, GA.

The chronic administration of sympathomimetic drugs, e.g., *d*-amphetamine and methylphenidate, has become a primary pharmacological treatment for children exhibiting the behavioral syndrome, Attention Deficit Disorder (ADD). The acceptance of this treatment strategy has derived largely from the outcome of case studies involving human children. However, variability in therapeutic efficacy suggests the need for an animal model that is more amenable to a systematic analysis of the variables that can influence drug effect. An interest in the behavioral effects of sympathomimetic and other stimulant drugs within a social context led us to undertake studies with group-living nonhuman primates to identify and characterize changes in several behavioral measures as a function of dose of *d*-amphetamine. In adult male stumptail macaques living within a heterogenous social group, *d*-amphetamine (0.003–0.56 mg/kg) decreased affiliative (prosocial) behavior. In contrast, *d*-amphetamine either increased or had little effect on aggressive behavior as a function of the monkey's dominance position in the group. Moreover, *d*-amphetamine increased aggression initiated by adult male monkeys against nonadult monkeys in the group and decreased aggression toward adult members. Also, the drug increased aggression toward kin-related members of the group and decreased aggression toward nonkin monkeys. The results indicate that *d*-amphetamine can modify the behavior of drug-treated members of a group, and that the drug can indirectly affect other members of the group even though they did not receive the drug. (Supported in part by USPHS grants DA-02128 and DA-01161, and NIH grant RR-00165 from the Division of Research Resources to the Yerkes Primate Research Center.)

ROLE OF BIOGENIC AMINES IN MAINTAINING HYPERACTIVITY IN NEONATAL RATS. Lewis S. Seiden. University of Chicago, Chicago, IL; Frederick E. Miller. University of Illinois, Chicago, IL; and Thomas G. Heffner. Parke Davis-Warner Lambert Drug Co., Ann Arbor, MI.

Monoamine neurotransmitters play an important role in the treatment and possible etiology of Attention Deficit Disorder with Hyperkinesis (ADDH). Evidence for the involvement of monoamines stems from both clinical work and studies exploring animal models of the ADDH syndrome. The primary pharmacological treatment of ADDH involves the use of sympathomimetic drugs such as *d*-amphetamine, methylphenidate and pemoline. The fact that these agents act to increase the synaptic concentration of monoamines has been one of the major reasons for the focus on monoamines in research on ADDH. Normally, rats are very inactive between 0 and 9 days postpartum. Between days 10 and 15, locomotion in the form of ambulation increases greatly, reaching a peak of activity on day 15, and between days 15 and 30, they gradually return to normal activity. However, when rats were depleted of forebrain dopamine by administration of the neurotoxin 6-hydroxydopamine (6-OHDA), the normal developmental pattern of locomotion was altered dramatically. Although the early developmental pattern was relatively normal, when the 6-OHDA rats reached the 15-day peak, their activity declined much more slowly, if at all, when compared to rats treated with vehicle. The degree to which the activity returned to normal depended on the extent of destruction of the catecholamine system. The results suggest relationships between the dopamine and serotonin systems in the expression of hyperkinesis and its treatment with amphetamine and related compounds.

AGGRESSION AND PROSOCIAL BEHAVIOR IN ADD CHILDREN: EFFECTS OF METHYLPHENIDATE. Stephen P. Hinshaw. University of California, Los Angeles, CA.

Stimulant medication, the most prevalent treatment regimen for Attention Deficit Disorder (ADD), has consistently been shown to reduce many of the core symptoms of the disorder, including problem behavior in the social realm. Yet two response domains that are of critical prognostic importance for children—prosocial behavior and aggression—are inconclusive with respect to medication response. First, although stimulants have repeatedly been shown to diminish socially disruptive and noncompliant behavior, their ability to decrease actual aggression has been demonstrated less