BEHAVIORAL ANALYSIS OF MARIJUANA EFFECTS ON FOOD INTAKE IN HUMANS. Richard W. Foltin and Marian W. Fischman. The Johns Hopkins University School of Medicine, Baltimore, MD.

Fifteen adult male research volunteers, in five groups of three subjects each, lived in a residential laboratory for up to 25 days. All contact with the experimenter was through a networked computer system, and subjects' behaviors, including food intake, were continuously recorded. During the first part of the day, subjects remained in their private rooms doing assigned work activities, and during the remainder of the day, they were allowed to socialize. In the first three experiments, a single cigarette containing active marijuana (1.84% Δ^9-THC, w/w) or placebo was smoked prior to the work period, and two or three cigarettes were smoked during the social access period. There was no effect of marijuana on food intake during the private period, but cigarettes smoked during the social access period increased total daily caloric intake by 20%. This increase was due to an augmentation of calories consumed as between-meal snack items rather than an increase in meal size per se. In the remaining two experiments, the type and variety of snack foods were increased, and the dose of marijuana was increased by having subjects smoke two cigarettes containing active marijuana (2.7% Δ^9-THC, w/w) or placebo during both the private work period and the social access period. Smoked active marijuana significantly increased total daily caloric intake by 40%. Once again, the increase in caloric intake was due to an increased consumption of snack foods rather than meals, but in this case increased food intake was evident during both private and social periods. The principal increase within the category of snack foods was in the intake of sweet solid items (e.g., candy bars) compared to sweet fluids (e.g., carbonated beverages), or savory solid items (e.g., potato chips). Increases in body weight during periods of active marijuana smoking were greater than predicted by caloric intake alone.

PRESIDENTIAL ADDRESS

Drug Reinforcement and Drug Abuse: From Laboratory to Clinic

George E. Bigelow, The Johns Hopkins University School of Medicine, Baltimore, MD

Chair: *Donald A. Overton,* Temple University, Philadelphia, PA

SYMPOSIUM

Opioid Agonists/Antagonists: Laboratory and Clinical Aspects

Chair and Discussant: *Linda A. Dykstra,* University of North Carolina at Chapel Hill, NC

INTRODUCTION. Linda A. Dykstra. University of North Carolina at Chapel Hill, Chapel Hill, NC.

In the last decade, a considerable amount of research has been devoted to developing opioid analgesics with a lower incidence of side effects such as respiratory depression, sedation and physical dependence. In this regard, the newly developed agonist/antagonists are of considerable interest due to their unique behavioral effects. For example, many of them produce analgesia, but have a reduced dependence potential when compared to morphine. In addition, investigations in man suggest that these compounds have potential in the treatment of chronic pain as well as in the treatment of opioid dependence. This symposium considered the behavioral pharmacology of some of these agents in nonhumans by presenting data about their effects in at least three different behavioral assays. These include (1) analgesic assays, (2) drug self-administration assays for examining reinforcing properties and (3) drug discrimination assays for examining a drug's stimulus properties. In addition to reviewing existing knowledge about the behavioral effects of opioid agonists/antagonists in animals, investigations about the behavioral effects of these agents in heroin-dependent individuals were discussed. Moreover, the use of opioids in the treatment of chronic pain was discussed with special emphasis on their potential for abuse in these situations.

REINFORCING AND DISCRIMINATIVE EFFECTS OF MU AGONISTS-ANTAGONISTS. Alice M. Young and Maureen A. Walton. Wayne State University, Detroit, MI; and Gail Winger. University of Michigan, Ann Arbor, MI.

The agonist-antagonist opioids are a heterogeneous group of compounds that display dissimilar constellations of agonist and antagonist effects. The behavioral pharmacology of agonist-antagonist opioids that exert mu agonist actions can be described in terms of the reinforcing and discriminative stimulus profiles of these compounds, with special emphasis on how these profiles may allow discrimination among compounds that differ in their efficacy as agonists. Studies of the reinforcing characteristics of selected mu agonists and agonist-antagonists have provided new evidence that maintenance of behavior under progressive-ratio procedures may require compounds with higher efficacy as agonists than does maintenance of behavior under fixed-ratio procedures. Specifically, full agonists such as codeine and alfentanyl can maintain performance under both procedures, whereas certain agonist-antagonists such as nalbuphine and buprenorphine maintain behavior under the fixed-ratio procedure but do not generate breaking points higher than those generated by saline under the progressive-ratio procedure. In addition, the discriminative profiles of selected agonist-antagonists provide evidence that generalization of stimulus control to different training doses of morphine can be indicative of agonist efficacy. Specifically, generalization to a higher morphine training dose may require greater efficacy than does generalization to a lower training dose. For example, a full agonist will generalize to both a lower and a higher morphine training dose, whereas certain agonist-antagonists will generalize only to the lower training dose, acting instead to antagonize control by the higher dose. Taken together, information about the discriminative and reinforcing characteristics of opiate agonist-antagonists may provide new leads in the search for analgesics with lowered abuse liability. (Supported by DA-03796 and DA-00254.)

ANALGESIC EFFECTS OF OPIOID AGONISTS AND PARTIAL AGONISTS IN MONKEYS. Charles P. France. University of Michigan School of Medicine, Ann Arbor, MI.

A tail withdrawal procedure similar to that described by Dykstra and Woods (1986) was used to study the analgesic effects of opioids in rhesus monkeys. The latency for monkeys to remove tails from 40°, 50° and 55°C water was compared among opioids that vary widely in receptor selectivity and efficacy. Some opioid agonists (e.g., alfentanyl, bre-

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-