National Institute on Drug Abuse

Research

monograph series

1

FINDINGS OF DRUG ABUSE RESEARCH

VOLUME 1

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An annotated bibliography of NIMH and NIDA-supported extramural grant research 1967-74 in two volumes

Volume 1

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National Institute on Drug Abuse
11400 Rockville Pike
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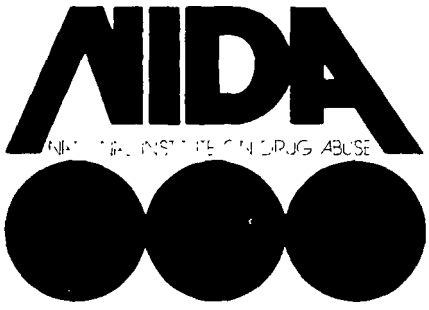

The NIDA Research Monograph Services is property by the Division of Research of the National Institute on Drug Abuse. Its primary objective is to provide critical reviews of research problem areas and techniques, the content of state-of-the-art conferences, integrative research reviews and significant original research. Its dual publication emphasis is rapid and targeted dissemination to the scientific and professional community.

NIDA RESEARCH MONOGRAPH series

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William Pollin, M.D. DIRECTOR, DIVISION OF RESEARCH, NIDA

Robert C. Petersen, Ph.D. EDITOR-IN-CHIEF

Eunice L. Corfman, M.A. EDITOR

Rockwall Building 11400 Rockville Pike Rockville, Maryland, 20852

PREFACE

Nearly eight years have elapsed since the inauguration of a high priority Federal research program directed toward better understanding and coping with drug abuse. When that program was begun, estimates of the extent of drug abuse were more frequently based on speculation than on hard data. The basic materials for studying such drugs as marihuana were frequently lacking and research was in its infancy. Opiate research, while it had a much longer history through pioneering work of the Addiction Research Center, the U.S. Public Health Hospitals at Lexington and Fort Worth a and other programs, also underwent a much needed expansion.

The research infant has now become a strapping adolescent. While much remains to be learned, this bibliography comprising some 3,500 titles and abstracts attests to the productivity of over 650 researchers whose work was directly supported through grants from the National Institute on Drug Abuse and its predecessor program in the National Institute of Mental Health. Its publication represents an attempt to give some sense of the diversity and scope of the Federal impact on drug abuse research. It is our hope that it will prove to be a valuable source of scientific information in itself and will also serve as a source document for later analysis of the Federal role in its extramural grant program towards shaping and contributing to the overall drug abuse literature.

Preparation of these volumes inevitably leaves us indebted to many individuals and organizations. First and foremost, special thanks are owed to the hundreds of researchers who took time from their busy schedules to give us detailed accounting of the papers they have published arising from our grant support. Without their generous cooperation a reasonably complete accounting would not have been possible. Thanks are also due to the staffs of some twenty libraries, information services and clearinghouses which provided assistance in many ways.

The actual production of the volumes demands thanks to many individuals whose commitment to the detailed preparation required testifies to their fine level of professionalism. Special thanks are due to the staff of Koba Associates, Inc., particularly to Georgette Semick, the project director, ably assisted by Carol Tuckerman and to their research assistants Tina Lindegren and Kath Nesper. Susan Lachter, Acting Chief of the National Clearinghouse for Drug Abuse Information here at NIDA provided necessary assistance as did other members of the NIDA staff.

Robert C. Petersen
Assistant Director, Research Division
NATIONAL INSTITUTE ON DRUG ABUSE

Introduction

PURPOSE

Since September, 1973, the Division of Research of the National Institute on Drug Abuse (NIDA) has been responsible for the coordination of extramural, grant-supported research into tke effects of drug use/abuse and for funding projects to examine possibe prevention and treatment modalities for its control. NIDA-supported work has its origins in the research program supported and coordinated since the 1960's by the National Institute of Mental Health. The bulk of the Federally funded research has been undertaken since 1967 and the results have been documented in numerous journals, books and other scientific publications.

A listing of published drug abuse literature including synopses of the content was considered necessary in order to provide NIDA with a resource for planning future research directions and for examining the impact of this literature on the scientific community. Thus, the purpose of tkis annotated bibliography is twofold: 1) to kelp NIDA program personnel review the findings of previous drug abuse grants in order to plan future research strategies, and 2) to serve as a retrospective indication of the findings from supported research that have been disseminated to the scientific community and the general public.

The publication, Findings of Drug Abuse Research 1967-1974, is a two-volume work that lists the drug abuse research literature supported by NIMH and NIDA and provides abstracts or summaries of the articles when these are provided by the author. Each volume may be used independently and each is indexed.

PREPARATION OF THE BIBLIOGRAPHY

Having defined the scope of the final product as research literature produced under NIMH-NIDA grants during the period 1967-1974. the first major task was to identify the relevant grants and their principal investigators (PIs). The methodology for collecting the materials was based on the assumptions that the Principal Investigator would, at minimum, be familiar witk the literature produced as a result of his/her grant and in most cases would also have copies of that literature. Lists of principal investigators were developed by utilizing NIMH and NIDA files of grantees and the Research Grants Index published by tire Public Health Service. Each identified Principal Investigator tken received a personally addressed letter explaining the project and requesting lists (and copies) of literature produced as a result of drug use/abuse grants for which s/he was designated as PI.

PIs were also asked to identify in a preliminary way which of ten program areas of drug use/abuse research would best classify their literature. By receiving this additional information from the PIs themselves, the project staff was provided with a firmer foundation for designing the final product.

The first request to PIs yielded an approximate 50 percent response rate within a period of one month. To augment, these responses the project staff sent outfollow-up reminders to non-respondents while concurrently contacting information resources such as the National Clearing House for Drug Abuse Information, the Student Association for the Study of Hallucinogens, Inc. (STASH) and the Addiction Research Foundation to obtain lists of articles/books published by those PIs who were not located by the principal contact method, Final response was from approximately 60 percent of all PIs. These' sources produced the remainder. To monitor tke communication with PIs and other information sources and to

organize information received, detailed recordkeeping systems were developed. File systems recorded the number of articles identified and submitted, classified or unclassified, and listed the literature identified but not accompanied by abstracts or articles. Literature received was checked for complete publication information and filed by its appropriate classification category.

Using the prepared resource list of rug abuse research and medical libraries, information services and clearinghouses, the project staff attempted to locate the several hundred articles which PIs identified but which were not forwarded or classified by the investigators. Once found, these were screened, classified and filed in accordance with project specifications.

Following the' collection of all identified articles and/or books, the final classification system and entry format were defined. Each entry was then formatted (accompanied by its author-prepared abstract or summary where available), cross-referenced where necessary and prepared for final submission to NIDA.

FORMAT AND ANNOTATION SYSTEM

In order to create a bibliography of optimal use, several questions were kept in mind throughout the design stages : "What format most readily would facilitate the bibliography's use ?" and "What information about each item is necessary for subsequent location by users?" These questions were carefull considered throughout the bibliography design process.

The format design reflects the bibliography's principal, in tended use (i.e., for program planning and evaluation) by organizing the material into program/ subject areas. Within each category the entries are organized alphabetically by author. To facilitate identification of new entries and location of cross-references, the author's(s') name(s) appears in capital letters. Publication and descriptive information about each item is provided in a standard bibliographic format which supplies information about the author(s) or editor(s), title of the chapter or article, source (book, proceedings or journal) including volume numbers and pages where applicable, book's publisher and dates of publication or presentation.

Following the entry's bibliographic information the author-prepared abstract or summary is included.

Whenever possible, author-prepared summaries, abstracts or short conclusions are used to describe the articles, books and proceedings. Since author-prepared abstracts are not always required by the publisher, both annotated and nonannotated citations are found in the bibliography. The intended use of the bibliography required that the findings be consistently validated. There fore, when no author-prepared abstract was available, the project staff did not attempt to summarize the findings. In the same vein, no attempt has been made to change or edit the abstracts and summaries for consistent language; thus, words such as 'our' and 'I' still remain.

Missing abstracts are not available for a number of reasons: the articles are out of print; literature is now "in press"; papers presented at meetings, conferences and symposia have not to date been published; short summaries were never required. In such cases the unannotated bibliographic information has, nonetheless, been provided.

CLASSIFICATION OF ENTRIES

The classification system was designed to dovetail with the-primary intended use of the bibliography; to review the progress of the NIMH-NIDA supported drug abuse research programs. Thus, the sections of the bibliography parallel the program areas of 'NIDA research: To determine whether the eleven categories are descriptive of the existing literature, the PIs were requested to indicate which of the suggested categories were most applicable for their articles and abstracts. Suggestions of alternative classification categories and systems were encouraged. A review of the replies received from the PIs showed that, for the most part, the program areas also adequately classified the grant-supported literature.

The ten subject-program categories that correspond with the first ten sections of the bibliography are:

I. Methodology of Drug Research
II. Drug Chemistry and Metabolism
III. Mechanisms of Action of Different Drugs
IV. Behavioral Studies

V. *Adverse Effects, Toxicity and Genetic Effects*
VI. *Drug Use/Abuse Prevention*
VII. *Treatment-Related Research*
VIII. *Psychosocial Studies*
IX. *Education*
X. *Epidemiological Studies and Surveys*

The eleventh section, "Peripherally Related", was included to list those materials that do not pertain exclusively to drug abuse research, but which are produced as an offshoot of NIMH and NIDA-supported drug abuse projects. For this reason entries in this category include references to subcategories such as therapeutic aspects of various abusable drugs, analytical techniques for more generalized behavioral research and the body's receptors for psychoactive drugs.

CROSS REFERENCES

Because many of the articles and books summarize findings related to several of the ten program areas, a cross-reference system was developed. In this way entries could be included in all relevant subject categories without duplicating the abstracts for each listing. The annotation for any cross-referenced entry can be found with the first citation. In subsequent categories the entry includes complete bibliographic information; however, for the abstract the reader is then referred to the earlier section.

INDEXES

To increase the usefulness of the bibliography, indexes have been provided for author/editor and for subject/drugs, So that the two volumes may be used independently, these indexes have been inserted at the end of both volumes. Virtually all index and cross references are to sections within the same volume.

CONTENTS OF VOLUME 1

The first volume of Findings of Drug Abuse Research offers three sections of entries pertaining to the methodology of drug abuse research and findings of basic research into the chemical and metabolic characteristics of drugs and their mechanisms of action.

CONTENTS OF VOLUME 2

The second volume of Findings of Drug Abuse Research includes entries on the behavioral and clinical aspects of drug abuse research including results of studies of adverse effects, prevention and treatment systems and the literature on human and psychosocial factors of drug abuse research (i.e., psychosocial studies, education and epidemiology of drug abuse).

The final section, entitled "Peripherally Related", contains findings from NIDA-supported drug abuse projects which do not pertain exclusively to that subject.

CONTENTS

VOLUME 1

VOLUME 2

I

Methodology of Drug Research

ABBOTT, S.R., ABU-SHUMAYS, A., LOEFFLER, K.O. and FORREST, I.S. High pressure liquid chromatography of cannabinoids as their fluorescent dansyl derivatives. Research Communications in Chemical Pathology and Pharmacology (in press)

Four different cannabinoids were converted to their 1-dimethylaminonaphthalene-5-sulfonate (dansyl) derivatives. Standard mixtures were separated by high pressure liquid chromatography and detected with an experimental filter fluorometer with sub-nanogram sensitivity. The effect of solvent properties on fluorescence spectra and quantum yields was also studied.

ABRAMS, L.A., GARFIELD, E. and SWISHER, J., editors. Accountability in Drug Education: A Model for Evaluation. Washington, D.C.: Drug Abuse Council, 1973.

ADLER, F.L. Detection of dependence-producing drugs in body fluids. World Health Organization Technical Report Series, No. 556. Geneva, Switzerland: World Health Organization, 1974.

ADLER, F.L. Drug testing by hemagglutination-inhibition. Immunoassays for Drugs Subject to Abuse. Edited by S.J. Mule, I. Sunshine, M. C. Braude and R.E. Willette. Cleveland, Ohio: Chemical Rubber Company Press, Inc., 1974. Pp. 37-43.

ADLER, F.L. and LIU, C-T. Detection of morphine by hemagglutination-inhibition. Journal of Immunology 106(6): 1684-1685 (1971)

The production of antibodies reactive with morphine and a radioimmunoassay sensitive to 0.5 ng of the drug has been described. This note confirms these findings and describes a rapid, simple and inexpensive hemagglutination-inhibition test of equal or greater sensitivity which appears to be adaptable to the screening of large numbers of urine specimens with a minimum of effort and equipment. The specific activities of methadone and of morphine were markedly different. Using one technique, morphine was 60,000 times more effective an inhibitor than methadone.

ADLER, F.L., LIU, C-T. and CATLIN, D.H. Immunological studies on heroin addiction. I. Methodology and application of a hemagglutination inhibition test for detection of morphine. Clinical Immunology and Immunopathology 1(1): 53-68 (1972)

Hemagglutination-inhibition techniques have been applied to measure morphine in sera and urines. A rapid screening test and a quantitative test, each capable of detecting 25 pg morphine, have been described. The former allows analysis of 50 specimens/hr, and both tests require only basic laboratory equipment. Methadone does not interfere; "false positive" reactions occur in urines from patients receiving codeine, meperidine, or dihydromorphinone. Dextromethorphan interferes slightly; diphenoxylate and dextropropoxyphene interfere slightly but not consistently. Ingestion of large amounts of poppy seeds results in positive urine tests. The applicability of hemagglutination-inhibition and other serological tests to the recognition of heroin abuse has been discussed. It is concluded that hemagglutination-inhibition merits consideration for the screening of specimens. and for the quantitation of morphine. The extreme sensitivity of hemagglutination-inhibition and other serological tests highly qualify these procedures for use as exclusion tests.

ADLER, F.L., LIU, C-T. and CATLlN, D.H. A rapid serological screening test for morphine. Federation Proceedings 31(2): 807 (March-April. 1972)

A hemagglutination inhibition test for the detection of morphine has been developed into a semi-quantitative rapid screening test that permits 50 analyses/hour/person. Serum from rabbits immunized with carboxymethylmorphine (CMM) - BSA and tanned sheep red blood cells coated with CMM-RSA are the test reagents. When adjusted to a lower sensitivity level of 50 nanograms morphine/ML urine, the test detects heroin use in serum for 36 hours and in urine for 72-96 hours after last admitted use of the drug. Methadone in customary maintenance doses does not interfere. Codeine reacts strongly and dextromethorphan weakly; the cross reactivity of these haptens with anti-CMM sera varies with individual animals, suggesting immunochemical complexity. Cross reactions also occur with meperidine, with aqueous extracts of poppy seeds and, to a lesser degree, with propoxyphene. It is recommended that this serological screening test be used for the purposes of determining heroin non-use rather than for proof of drug abuse.

ADLER, M.W., LIN, C., SMITH, K.P., TRESKY, R. and GILDENBERG, P.L. Lowered seizure threshold as a part of the narcotic abstinence syndrome in rats. Psychopharmacologia 35: 243-247 (1974)

A decrease in threshold to flurothyl-induced seizures in rats is a sensitive measure of the morphine primary abstinence syndrome. The test is easy to perform, yields highly reproducible results, allows for simple statistical group comparisons and correlates well with the usual methods of assessing withdrawal.

AGHAJANIAN, G.K. and BUNNEY, B.S. Central clopaminergic neurons: Neurophysiological identification and responses to drugs. Frontiers in Catecholamine Research. Edited by E. Usdin and S.H. Snyder. New York: Pergamon Press, 1973. Pp. 643-648.

By combined neurophysiological and histochemical methods, dopaminergic neurons of the zona compacta (ZC) of the substantia nigra and the adjacent ventral tegmental (VT) areas were found to be clearly distinguishable from adjacent non-dopaminergic neurons such as zona reticulata (ZR). Of particular interest was the finding that ZC and VT cells are inhibited by microiontophoretic doparnine (DA) but are insensitive to acetylcholine. On the other hand, ZR neurons are relatively insensitive to DA but are excited by acetylcholine at very low ejection currents. This suggests that if there are cholinergic afferents to the substantia nigra they would need to impinge upon ZR rather than upon ZC cells to produce a physiological effect. Drugs which either increase DA availability at DA receptors such as amphetamine or have a direct DA agonist action such as apomorphine inhibit the firing of dopaminergic neurons; these results are consistent with the operation of a compensatory negative feedback system. Conversely, presumed DA receptor blockers are consistent with the operation of a compensatory positive feedback system. The soma of dopaminergic neurons appear to have DA receptors since they are responsive to the direct, microiontophoretic application of either DA or the DA agonist apomorphine. If the terminals of dopaminergic neurons also have such DA receptors, presynaptic DA receptors then this might explain the postulated receptor mediated feedback control of striatal tyrosine hydroxylase activity at dopaminergic synapses.

ALTSHULER, H.L. and BURCH, N.R. Period analysis of the electroencephalogram of subhuman primates. Behavior and Brain Electrical Activity. Edited by N.R. Burch and H.L. Altshuler. New York: Plenum Press, 1974.

These studies demonstrate that closely related pairs of drugs, cocaine versus d-amphetamine and chlorpromazine versus pentobarbital, may be distinguished from one another on the basis of the period-analytic descriptors of the EEG. The differences observed were in both magnitude and direction of change. In addition, different EEG characteristics in response to high or low doses or pentobarbital were clearly observed. These preliminary studies suggest that the period-analytic methodology should prove useful in future, more detailed studies of the mechanism of action of these and other centrally active drugs.

BADEN, M.M., VALANJU, N.N., VERMA, S.K. and VALANJU, S.N. Confirmed identification of biotransformed drugs of abuse in urine. American Journal of Clinical Pathology 57(1): 43-51 (January, 1972)

A procedure that has been developed over a 6-year period at the office of chief medical examiner in New York City for rapid routine identification of drugs of abuse in urine is described. The urine is extracted at acidic, strongly basic, and weakly basic ph: the last, ph 8. 5, fraction is hydrolyzed to increase extractable morphine and codeine. The residues are subjected to thin layer chromatography and suspected spots scraped from the plates and confirmed by microcrystal examination or spectrofluorometry. Amphetamines, quinine, methadone, meperidine, propoxyphene, pentazocine, cocaine, and phenothiazine are present in the strongly basic extract. The acidic drugs, in particular barbiturates and glutethimide, are confirmed by gas liquid chromatography. This procedure has proved effective for the routine analysis of more than 300 urine specimens daily for court purposes as well as for a variety of drug abuse identification, treatment, and followup programs. A rapid sensitive microchromatographic method for detection of marihuana components from teeth and fingers is also described.

BAILEY, D.N. and JATLOW, P.I. Methaqualone, a new drug of abuse: Studies of analytical methodology and interpretation of serum drug levels in overdose. Clinical Chemistry 19: 666 (1973)

Methaqualone intoxication is being seen in epidemic proportions in out community. Serum drug levels were determined in 15 documented cases of methaqualone overdose seen at our medical center from June to December 1972. Analyses were performed by gas-liquid chromatography (GLC) by a modification of the method of Berry (J. Chromatogr. 42, 39, 1969) and by ultraviolet spectrophotometry (UV) using both chloroform and hexane extraction. Levels obtained by GLC were significantly lower than those obtained by UV following chloroform extraction but correlated well with those following hexane extraction. Our studies of serum and urine indicate that at least one chloroform extractable methaqualone metabolite has an ultraviolet spectrum similar to that of the unchanged drug. This may in part explain the higher results obtained by ultraviolet spectrophotometric analysis using a more polar solvent (chloroform) and may also account for discrepancies in the literature. This study emphasizes the importance of proper choice of solvent in the ultraviolet determination of methaqualone.

Since ultraviolet spectrophotometric analysis using hexene extraction followed by back extraction into 1 N hydrochloric acid yields results that are equal to those obtained by GLC, it presumably measures only unchanged drug. This procedure is suitable for emergency use.

Following methaqualone overdose, levels of unchanged drug in serum ranged From 0.2 mg/100 ml to 2.2 mg/100 ml; levels above 0.8 mg/100 ml were usually associated with coma in this series. All patients recovered with supportive therapy only.

BAILEY, D.N. and JATLOW. P.I. Methaqualone overdose: Analytical methodology, and the significance of serum drug concentrations. Clinical Chemistry 19: 615-629 (1973)

Methaqualone abuse and overdose have recently become “epidemic.” We determined concentrations of The drug in scrum in 15 cases of overdose by gas-liquid chromatography (GLC) and ultraviolet spectrophotometry (UV). Values by GLC were consistently lower than those determined by UV after chloroform extraction, but correlaled well with those obtained by UV after hexane extraction. Our studies show that at least one chloroform extractable metabolite has a spectrum very similar to that, of the parent drug, This may in part explain the lower results obtained by GLC and suggests that other reported data based on UV analysis of chloroform and ether extracts may be too high. Extraction with hexane, a less polar solvent, followed by back extraction into HCL provides an accurate UV method suitable for emergency use. Concentration of unchanged methaqualone in serum after overdose ranged from 2 mg/liter to 22 mg/liter in this series; those greater than 8 mg/liter were usually associated with unconsciousness.

BALL, J.C., ENGLANDER. D.M. and CHAMBERS, C.D. The incidence and prevalence of opiate addiction in the United States. The Epidemiology of Opiate Addiction in the United States. Springfield, Illinois: Charles C. Thomas, 1970. Pp. 68-78.

A method for estimating the extent of opiate addiction in the U.S. is described. It is based upon a combination of the 3 most comprehensive sources of data pertaining to addicts, that of the Bureau of Narcotics, the New York City Narcotics Register, and the hospitals. A separate method for calculating the incidence and the prevalence of addiction was derived. These estimation procedures can he employed for any recent time period, and they are subject to verification. In 1967 it was calculated that there were 108,424 known opiate addicts in the U.S. Of this number, 30,885 were first reported during 1967.

BARRY, H. Classification of drugs according to their discriminahle effects in rats. Federation Proceedings 33(7): 1814-1824 (July, 1974)

Drugs were classified according to their discriminable effects in rats. A discriminative response was established by differential reinforcement in a series of training sessions under the drug and nondrug conditions or under 2 different drugs. Drug conditions with stimulus characteristics resembling one of the training conditions were identified by consistent choice of one of the alternative responses during tests under novel doses or drugs. These tests of discriminative stimulus properties have identified the following categories of drugs. 1) Central sedatives, including barbiturates and the minor tranquilizers (chlordiazepoxide and meprobamate); 2) Central anticholinergics (antimuscarinics); 3) nicotine; 4) marihuana or its component delta-9-tetrahydrocannabinol; and 5) hallucinogens (mescaline, LSD). Drugs with apparently weaker discriminahle effects include 1) chlorpromazine and the other phenothiazines; 2) amphetamine; and 3) morphine. The discriminative stimulus seems to be a central drug effect, and the differential response is difficult to estahlish with peripheral drug effects.

BENTLER. P.M. and EICHBERG, R.H. A social psychological approach to substance abuse construct validity: Prediction of adolescent drug use from independent data sources. Presented at the National Institute on Drug Abuse Drug Lifestyles Conference, St. Simons, Georgia, January, 1975.

Some metatheoretical and metaempirical issues in predictive drug abuse research are reviewed first. The relation of ethics to research in this area, the importance of possible future applied uses of the research, the role of discriminant validation in prediction, and the relevance of research to public policy are considered. The criterion to he predicted is discussed in the context of decisions that need to be made with respect to its univariate or multivariate nature, the measurement of use vs. abuse, the possible role of variables correlated with use, and the importance of operational definitions. Structural considerations related to the measurement of predictors are discussed next, as related to measures obtained by self-report, peer and parent-report, behavior observation, performance testing, psychophysiological methods, archives, and sociological procedures. Principles of prediction relevant to the design of research in this area are reviewed in the next section. Finally, empirical drug research using independent peer and parent data sources is reviewed for its relevance to future NIDA predictive research.

BEN-ZVI. Z., MECHOULAM, R. and BURSTEIN, S. Identification through synthesis of an active delta-1(6)-tetrahydrocannabinol metabolite. Journal of the American Chemical Sociey 92: 3468-3469 (1970)

BLACKFORD, L.S-C. Surveillance of levels of drug use in a student population. Drug Forum 1(3): 307-313 (April, 1972)

A method of developing comparable rates of drug use in student populations is outlined. Tested by five large surveys, a set of standardized methods, procedures and forms makes it possible to produce such information with a minimum of time and money. The comparability of survey results between years or between areas is stressed.

BONNET, K. A. and PETERSON, K. E. A modification of the jump-flinch technique for measuring pain sensitivity in rats. Pharmacology Biochemistry and Behavior (in press)

The jump-flinch procedure provides a sensitive alternative to the hot-plate and tail-flick procedures. Analysis of the components of motor responses to increasing intensity of foot shock presentation has allowed the observational discrimination of five reliably elicited categories of unlearned responses to inescapable foot shock. Morphine sulfate differentially altered response category thresholds in rats. Response category thresholds also differed between Wistar and Fisher strain rats in analgesic effects of morphine sulfate.

BORGATTA, E.A., LEVENTHAL, H., RITTENHOUSE, J. and BALL, S. Symposium: Problems in Evaluation Research of Drug Information Programs. Report to the National Academy of Sciences, 1973.

BORGEN, L.A. and DAVIS, W.M. Vehicle and route of administration as parameters affecting operant behavioral effects of delta-9-tetrahydrocannabinol. Journal of Pharmaceutical Sciences 62(3): 479-480 (March, 1973)

Four vehicles for delta-9-tetrahydrocannabinol were compared after intraperitoneal and subcutaneous administrations, using the disruption of food-reinforced, operant behavior of rats as the test system for cannabinoid activity. Aqueous suspensions based on polyvinylpyrrolidone, polysorbate 80, and a polysorbate 65-sorbitan monolaurate combination all were effective vehicles for intraperitoneal or subcutaneous absorption of the cannabinoid. An olive oil solution was poorly effective. The polyvinylpyrrolidone dispersion appeared to have the most rapid onset of action, while the polysorbate 65-sorbitan monolaurate combination had the longest duration of action.

BRADY, J.V., GRIFFITHS, R. and WINGER, G. Drug-maintained performance procedures and the evaluation of sedative hypnotic dependency potential. Presented at the Upjohn Conference on Hypnotics, Kalamazoo, Michigan, July, 1974.

Behavioral procedures for evaluating the abuse potential of pharmacological agents have received increasing experimental attention over the past decade since the publication of the classic drug self-infusion studies in the early 1960's (Weeks, 1961). For the most part, methodological developments have focused upon the assessment of a broad range of chemical substances in laboratory animals under conditions which provide continuous access to the drug (Schuster and Thompson, 1969). and a high correlation between the compounds self-administered under such conditions and those abused by man has been demonstrated (Schuster and Balster, 1973). Of more recent interest has been the concern with evaluations of a given drug's abuse liability relative to the range of compounds with demonstrated dependency potential, and with procedures for ordering the reinforcing properties of such compounds. Behavioral assessment techniques previously developed for measuring the differential reinforcing effects of stimuli other than drugs have begun to be applied to the determination of the relative reinforcing properties of various doses of a single compound, as well as to the rank ordering of different compounds. In general, experimental drug self-administration approaches to the problem have focused upon three broad performance measurement categories: 1) relative rates of responding; 2) progressive ratio or "response cost" values; and. 3) preference or choice determinations.

BRAESTRUP, C. Gas chromatographic evidence for the presence of 3-methoxy-4-hydroxyphenylethanol in rat brain. Biochemical Pharmacology 21: 1775-1776 (1972)

BRAESTRUP, C. Identification of free and conjugated 3-methoxy-4-hydroxyphenylglycol (MOPEG) in rat brain by gas chromatography and mass fragmentography. Analytical Biochemistry 55: 420-431 (1973)

BRAESTRUP, C. 3-Methoxy-4-hydroxyphenylethanol in the rat brain. Journal of Neuropharmacology 20: 519-527 (1973)

The neutral dopamine metabolite, 3-methoxy-4-hydroxypenylethanol (MOPET) can be measured in the rat brain by a GLC method using a pentaflouropropionic derivative and electron capture detector. The identity of MOPET is verified by mass spectrographic analyses.

The endogenous level of MOPET of 16.6 ng/g whole rat brain can be raised more than four-fold by intraperitoneal injection of L-DOPA, dopamine or MOPET. In contrast intraventricular injection of dopamine or intraperitoneal injection of L-DOPA plus a peripheral decarboxylase inhibitor (Ro 4-4602), results in small and insignificant increase of MOPET in the CNS.

It is concluded that MOPET is probably of low significance to central dopamine metabolism and that MOPET found in the rat brain is predominantly of peripheral origin.

BRATTIN, W.J. and SUNSHINE, I. Immunological assays for drugs in biological samples. American Journal of Medical Technology 39(6): 223-230 (June, 1973)

A number of immunological assay systems for the detection of drugs of abuse in biological samples have become commercially available recently. The general theory of immunological assays and the specific principles of each assay are discussed. The advantages and limitations of these methods with respect to non-immunological techniques are also discussed, and some of the important features of the immunoassays (sensitivity, reliability, cost, speed) are compared.

BROCHMANN-HANSSEN, E. Opium alkaloids XII: Quantitative determination of morphine in opium by isotope dilution. Journal of Pharmaceutical Sciences 61: 1118-1119 (1972)

A method was developed for quantitative determination of morphine in opium based on the isotope dilution technique. Morphine-2-^{3}H and morphine N-$^{14}CH_3$ are used as radioactive standards. A mixture of opium and the radioactive morphine standard is triturated with dimethyl sulfoxide, dispersed on diatomaceous earth and acidic aluminum oxide, and suspended in water. The aqueous suspension is transferred to a chromatographic column of acidic aluminum oxide, and the alkaloids are eluted with water. Alternatively, the mixture of opium and radioactive morphine is triturated with a little water and dispersed on diatomaceous earth, and the alkaloid bases are liberated with ammonia. The powder mixture is transferred to a column of neutral aluminum oxide and eluted with chloroform-isopropyl alcohol (3:1). Phenolic and nonphenolic alkaloids are separated by extraction at pH 13, and morphine crystallizes from the aqueous phase after adjustment of pH to 9. The crystals are collected and recrystallized to constant radioactivity. Both extraction methods gave the same results. No loss of tritium occurred during the assay, and morphine-2-^{3}H and morphine-N-$^{14}CH_3$ were equally satisfactory as radioactive standards. The method is specific for morphine, has good precision (0.4%), and requires no elaborate technique.

BROCHMANN-HANSSEN, E., CHEN, C.H., CHIANG, H.C., FU, C-C. and NEMOTO, H. Opium alkaloids XIV: Biosynthesis of aporphines -- detection of orientaline in opium poppy. Journal of Pharmaceutical Sciences. 62(8): 1291-1293 (August, 1973)

Orientaline was detected in the opium poppy by an isotope dilution method based on its biosynthesis from norlaudanosoline. Administration of labeled orientaline revealed that this alkaloid was not a precursor of isoboldine, and the experimental results provided no evidence for a pathway involving norprotosinomenine. No conclusion was possible relative to the origin of magnoflorine in the opium poppy.

BROCHMANN-HANSSEN, E., FU, C-C. and ZANATI, G. Opium alkaloids IX: Detection of coreximine in papaver somniferum L. Based on its biosynthesis from reticuline. Journal of Pharmaceutical Sciences 60(6): 873-876 (June, 1971)

Protoberberines are biosynthesized in plants from reticuline in such a way that the N-methyl group of reticuline becomes the methylene group in the 8-position. It was demonstrated in this study that coreximine, a tetrahydro-psi-berberine, is also derived from reticuline. (±)-Reticuline-(3-^{14}C) administered to intact opium poppies was incorporated into coreximine to an extent of 0.174% and controlled degradation showed that the radioactivity was located at the C-6 position. Consequently, it could be concluded that the opium poppy is capable of converting reticuline to coreximine, and that coreximine, like scoulerine and isocorypalmine, is a normal member of the opium alkaloids. In the same way, it was shown that canadine, tetrahydropalmatine, stylopine, and berberine were not present in the plants in detectable amounts.

BROCHMANN-HANSSEN, E., LEUNG, A. T. and RICHTER., W. J. Opium alkaloids XIII. Isolation of 160 hydroxythebaine. Journal of Organic Chemistry 37: 1881 (1972)

The hydrophenathrene alkaloids of opium have been studied extensively, and their biosynthesis in the living plant has been established in considerable detail. Investigation of the minor alkaloid constituents of opium has led to the isolation of a new alkaloid of this group. It was isolated from the nonphenolic alkaloid fraction of opium and purified by preparative thin-layer chromatography (TLC) on a sicica gel and by column chromatography on neutral aluminum oxide.

BURKS, T.F. Vascularly perfused isolated intestine. Proceedings of the 4th International Symposium on Gastrointestinal Motility, Banff, Alberta, Canada, September 6-8, 1973.

Segments of dog, cat or monkey small intestine were vascularly perfused in vitro with a physiological salt solution. Motility was measured by intraluminal balloons or open catheters or by extraluminal strain gages. All three methods gave similar results. The isolated segments maintained viability, judged by electrical and motor activity and responses to drugs, for up to several hours of isolation. Reasonably reproducible graded responses to stimulatory agonists were obtained. Quantitative responsiveness to stimuli remained stable for at least 0. 5 hr. This preparation is offered as a simple and economical technique for in vitro studies with the intestine.

BURSTEIN, S. and ROSENFELD, J. The isolation and characterization of a major metabolite of delta-1-THC. Acta Pharmaceutica Suecica 8:699 (1971)

The purpose of the experiments reported here is the identification of the urinary metabolites of delta-1-THC. These results are a continuation of this project in our laboratory, some of which have been previously reported. These findings suggest the possibility than an aldehyde may be an intermediate between 7-OH-delta-1-THC and the acid. The sensitivity of the conjugates to base indicates that they may be either esters or amides.

BUSH, M. T. and SANDERS-BUSH, E. Phenobarbital, mephobarbital, and metharbital, and their metabolites. Chemistry and methods for determination. Antiepileptic Drugs. Edited by D. M. Woodbury, J. K. Penry and R. P. Schmidt. New York: Raven Press, 1972. Pp. 293-302.

Those barbiturates which are important anticonvulsants (phenobarbital. mephobarbital, and metharbital) have structural similarities to a number of other classes of anticonvulsants (the hydantoins and oxazolidinediones), as well as to primidone. The chemical and physical properties of all of these compounds have enough in common to require that procedures for their detection and quantitation be carefully designed in order to minimize interference. It seems desirable, therefore, to discuss those physicochemical properties which are important in the present context, so far as the available data permit.

These properties are basic to all of the methodologies which have been developed for the separation, identification, and quantification of these drugs. The subsequent discussion of methodologies will involve their careful consideration.

CASHAW, J.L., McMURTHEY. K.D., BROWN, H. and DAVIS, V.E. Identification of catecholamine-derived alkaloids in mammals by gas chromatography and mass spectrometry. Journal of Chromatography 99: 567-573 (1974)

Tetrahydropapaveroline. the tetrahydroisoquinoline alkaloid derived from dopamine, is converted in vivo by rats and by rat-liver and brain preparations to tetrahydroprotoberberine alkaloids. The latter alkaloids have also been identified for the first time in the urine of parkinsonian patients receiving L-DOPA therapy. These findings suggest that man, like plants, may have the ability to elaborate several classes of alkaloids with potentially important pharmacological consequences.

CASHAW, J.L., WALSH, M.J., YAMANAKA, Y. and DAVIS, V.E. Simultaneous determination of biogenic amines and narcotic alkaloids by gas-liquid chromatography. Journal of Chromatographic Science 9: 98-104 (February, 1971)

A GC method has been developed for the simultaneous determination of catecholamines. simple tetrahydroisoquinolines, a complex benzyltetrahydroisoquinoline alkaloid as well as the phenanthrene (opium) alkaloids. These chemical classes of pharmacologically active bases were separated and identified as trimethylsilylether derivatives on a six ft. 3% OV-1 column. Morphine, normorphine, and codeine were completely separated from each other as well as from their biosynthetic precursor in the opium poppy. tetrahydropapaveroline (THP). Additionally, THP is a known alkaloid metabolite of the neuroamine, dopamine, in animal systems. By this procedure dopamine. its O-methylated metabolite 3-methoxytyramine. a simple isoquinoline alkaloid derivative of dopamine formed by condensation with acetaldehyde salsolinol, and THP, as well as the narcotic alkaloids could be analyzed on a single sample, This method should be of general applicability to several diverse biomedical problems. GLC analysis of these compounds would be useful in such areas as alkaloid metabolism in plant and mammalian systems. drug abuse detection. biogenic amine metabolic pathway studies, investigations involving the interaction of narcotic alkaloids with neurotransmitter stores, and especially in alcoholism research concerning the interaction of alcohol with neuroamine metabolism.

CATLIN, D.H., ADLER, F.L. and LIU. C-T. Immunological studies on heroin addiction. II. Applications of a sensitive hermagglutination-inhibition test for detecting morphine to diagnostic problems in chronic heroin addiction. Clinical Immunology and Immunopathology 1(4): 446-455 (1973)

A sensitive hemagglutination-inhibition (HI) assay has been applied to the detection of morphine (morphine equivalents) in urine or serum. Samples obtained from 117 known chronic heroin addicts were analyzed in a clinical trial. Positive results were found in 98% of urine samples collected between 3 and 48 hr after the last admitted use of heroin, while of those analyzed by the less-sensitive thin-layer chromatography only 56% were positive for the same time interval. The extreme sensitivity of HI and other serological tests highly qualify these procedures for excluding the possibility of recent heroin use. It is concluded that HI merits consideration for the screening of urine or serum for morphine. The significance of the findings with regard to the diagnosis of chronic heroin addiction is discussed.

CHATTERJIE. N., FUJIMOTO, J.M., INTURRISI, C.E., ROERIG. S., WANG. R.I.H., BOWEN. D.V., FIELD. F.H. and CLARKE, D.D. Isolation and stereochemical identification of a metabolite of naltrexone from human urine. Drug Metobolism and Disposition 2(5): 401-405 (1974)

Pooled urine samples from patients receiving 100-200 mg of naltrexone per day orally were extracted; the basic (alkaloid) compounds derived were isolated by preparative thin-layer chromatography. The major metabolite of naltrexone was found to be an epimer of N-cyclopropylmethyl-14-hydroxy-7, 8-dihydronormorphine wherein the 6-keto group of naltrexone had been reduced to yield the 6 beta-hydroxy epimer (an isomorphine). This conclusion was based on infrared, mass, and nuclear magnetic resonance spectra studies. Furthermore, the reduction product formed in vitro in a soluble chicken liver enzyme system from naltrexone and an in vivo metabolite of naloxone derived from the chicken were found to have the more commonly expected 6 alpha-hydroxy orientation.

CHATTERJIE. N., INTURRISI. C.E., FUJIMOTO, J.M. and ROERIG. S. Species variation in the stereochemistry of a metabolite of naltrexone. The Pharmacologist 16(2) (Fall. 1974)

A major metabolite of naltrexone (I), isolated from human urine was found to be an epimer of N-cyclopropylmethyl-14-hydroxy-7, 8-dihydronormorphine or EN-2260 (II), wherein the 6-OH group was found to be beta due to metabolic reduction of the 6-keto group of I. This conclusion was based on infrared, mass and nuclear magnetic resonance (NMR) spectra studies. The reduction product of I obtained in vitro using a soluble liver enzyme system derived from the chicken was found to have a 6 alpha-OH orientation as in II. while that product from the rabbit was found to have a 6 beta-OH orientation similar to the stereochemistry of the human metabolite or I. The rabbit liver enzyme system reduces naloxone to the corresponding 6 beta-OH metabolite. The in vivo reduction product of naloxone isolated from chicken urine was found to be the 6 alpha-OH metabolite. These data demonstrate species of differences in the metabolism of these narcotic antagonists.

CHOULIS, N.H. and PAPADOPOULOS, H. Gas chromatographic determination of methadone sustained release tablets. Journal of Chromatography (in press)

CICERO, T.J. and MEYER, E.R. Morphine pellet implantation in rats: Quantitative assessment of tolerance and dependence. The Journal of Pharmacology and Experimental Therapeutics 184(2): 404-408 (1973)

The development of tolerance to and physical dependence on morphine was quantitatively examined in rats implanted s. c. with 75-mg morphine pellets. The animals were maintained for up to seven days after pellet implantation and tolerance and physical dependence were assessed at daily intervals. Both tolerance and dependence peaked after three days of pellet implantation and then declined gradually after this time. The withdrawal reaction precipitated by naloxone in morphine-dependent rats was characterized by lacrimation. salivation, an ejaculate-like discharge, diarrhea, hyperactivity and most notably by wet-dog shakes. Since the observed withdrawal syndrome included virtually every response which had previously been associated with morphine abstinence in the rat, it appears that morphine pellet implantation produces a degree of physical dependence which is at least as great as that which can be obtained with more commonly used techniques. On the basis of these data, it was concluded that the technique of pellet implantation can be used in the rat as a rapid and reliable means of producing a high degree of tolerance and physical dependence on morphine which are readily quantifiable.

COCHIN, J. Methods for the appraisal Of analgesic drugs for addiction liability. Selected Pharmacological Testing Methods, Vol. 3. Edited by A. Burger. Medicinal Research Series. New York: Marcel Dekker. Inc., 1968.

The efforts of many investigators, especially those at Lexington and Ann Arbor, have resulted in methods which permit valid assessments and judgments to be made regarding the physical-dependence liability, and more recently the psychological-dependence liability, of new therapeutic agents. Until the day comes when we have analgetic agents without addiction liability, these methods will perform a necessary and useful function despite the limitations of their highly specialized nature and their high cost in time, effort, and money.

COCHIN, J. The use of the animal model in assessing analgesic potency and dependence liability. Research Animals in Medicine. Washington, D.C.: National Heart and Lung Institute, NIH, HEW (Publication no. 72-333). Pp. 701-707.

There is no question that the use of animal models will permit investigators to study, assess and evaluate many facets of the phenomenon of addiction in animals which we were not able to do previously. It is quite possible that the importance of evaluation of subjective drug effects will decrease as such animal techniques become more refined and sophisticated and this is, after all, what animal models are for--to avoid doing in man what can be done in animals and to help us to understand what happens in man.

COHEN. M. and KLEIN, D. F. A measure of severity of multi-drug use among psychiatric patients. International Pharmacopsychiatry 6:83-91 (1971)

A method for measuring the severity of multi-drug use among psychiatric patients has been developed which takes into consideration the three basic criteria of drug abuse; number of different drugs used, frequency of use and length of use. The procedure initiated with several mental health professionals rating the drug-use patterns of 117 young psychiatric patients with a history of drug abuse. These ratings were then used to develop scoring criteria for each individual drug and combinations of drugs. The final result is a method which systematically categorizes drug users as either mild, moderate or heavy users.

COUSSENS, W.R., CROWDER, W.F. and DAVIS, W.M. Morphine induced saccharin aversion in alpha-methyltyrosine pretreated rats. Psychopharmacologia 29: 151-157 (1973)

Rats pretreated with L-alpha-methyltyrosine (AMT) and then given pairings of saccharin drinking and morphine infusion subsequently showed a reduced preference for saccharin over water, when compared with control rats. Control conditions were AMT pretreatment with saccharin-saline pairings, saline pretreatment with saccharin-morphine pairings, and saline pretreatment with saccharin-saline pairings. A second experiment also showed significantly greater saccharin aversion with morphine-infused, AMT-pretreated rats than with saline-infused AMT-pretreated rats although the morphine dosage was lower than that used in Experiment 1. These results suggest that morphine is aversive to rats that have been treated with AMT.

DAVIDOW, B. Drug testing: A little urine goes a long way. Medical Laboratory Observer 40 (September-October, 1971)

DAVIDOW, B., LIPETRI. N. and QUAME, B. A thin-layer chromatographic screening procedure for detecting drug abuse. American Journal of Clinical Pathology 50(6): 714-719 (December, 1968)

An efficient screening procedure for the detection of drug abuse is described. Using a single solvent system, acidic (barbiturates), neutral (glutethimide), and basic drugs (morphine, amphetamine), are extracted simultaneously from urine. The drugs are separated by means of thin-layer chromatography, using a single developing solvent, and are made visible by spraying with a series of compatible chromogenic reagents. The method is rapid, sensitive, and suitable for screening a large number of specimens.

DAVIDOW, B. and QUAME, B. Extraction of drugs from urine using disposable chromatographic columns. The Pharmacologist 13: 309 (1971)

The increasing demand for drug screening analysis has stimulated investigation directed toward the development of more efficient detection methods. Using a commercially available disposable chromatographic column, drugs such as amphetamines, barbiturates, morphine, methadone. and quinine could be extracted from urine and subsequently eluted with an organic solvent. The column could also be used for the serial sampling of an individual's urine over a period of time. In this manner a single analysis would indicate whether an individual has taken drugs during this time period. The commercial columns were found to be convenient, rapid to process and equivalent in sensitivity to the conventional extraction procedures. In addition, columns containing the extracted drugs were easier to transport to the laboratory than were the urines.

DAYTON, H.E. and INTURRISI, C.E. Urinary excretion of naltrexone and its metabolites in man, rabbit, monkey and rat. Federation Proceedings 34 (1975)

A GLC method has been developed for the simultaneous determination of Naltrexone (I). 6-beta-OH Naltrexone (II) and B-alpha-OH Naltrexone (III) as the TMS-derivatives. Analysis of urine from rabbit, monkey and rat demonstrate that, like man, these species reduce I to II but not I to III. In three Naltrexone maintenance patients (125 mg., p.o., 3x/wk.) an average of 37% of a dose was recovered in the 48 hour urine as free I (0.8%). conjugated I (7.6%), free II (16.8%) and conjugated II (11.8%). Approximately 34% of the dose appeared in the urine during 0-24 hours with only 3% recovered during 24-48 hours. The ratio of II/I rose from 2 at 0-4 hours to 34 at 24-48 hours post drug. In a rabbit given 30 mg/kg/day (i.p.) for 4 days, 9.7% of the daily dose was recovered in the 24 hour urine as free I (0.1%), conjugated I (7.6%). free II (0.15%) and conjugated II (1.9%). The ratio of II/I rose from 0.1 at 0-4 hours to 2.7 at 20-24 hours post drug. In monkeys given 30 mg/kg (p.o. or s.c.) the ratio of II/I increased 10-fold from 0.6 at 0-4 hours to 6.0 at 24-36 hours post drug. Thus, in man and monkey, II is the predominant and persistent urinary metabolite.

DeCATO, L., JR. and ADLER, F.L. Recurrence of morphine excretion after single and multiple dose administration. Federation Proceedings 33(3): 473 (March, 1974)

Extended urinary excretion patterns for morphine HCL (MO) were studied by means of hemagglutination inhibition (HI). This immunologic technique can detect the presence of MO plus antigenically similar metabolites (morphine equivalents (ME)) with NG/ML sensitivity. Assays of individual 24 hr urine specimens from 16 Swiss Webster mice after single i.p. injections of MO showed a rapid decline in ME/ML to below HI sensitivity levels within 4 days. Administration of naloxone HCL to 8 mice on day 6 did not increase their ME excretion. Between days 10-13 about 20 percent of the mice exhibited a recurrence of ME excretion which was not dependent upon prior naloxone treatment. More complex excretion patterns were noted after multiple increasing MO injections. A rapid decrease in ME/ML over the first 4 days after cessation of injections was followed by a slowly declining plateau for 14 days. Approximately 40 percent of the 16 mice exhibited large sporadic increases in ME excretion starting 10 days after the first MO injection. The results suggest that MO or antigenically related metabolites are sequestered and sporadically released for long time periods and that this could have significance for current concepts of opioid tolerance.

DeFLEUR, L.B. Biasing influences on drug arrest records: Implications for deviance research. American Sociological Review (February, 1975)

Despite repeated demonstrations that a variety of factors bias official records. such records are widely used in deviance research. The crucial issue relating to such use is whether biasing factors are random (tending to cancel each other out) or systematic (reducing validity for research to unacceptable degrees). Deviance statistics are generated in contexts whose numerous biasing factors can distort the occurrence rates of deviant acts. This study examines the influence of such factors on drug arrest records in Chicago. Three decades of arrests were studied and related to findings from extensive field research in the Narcotics Division of the Chicago Police. Drug arrest statistics for both whites and nonwhites revealed distinct trends and distributions over time and space. These patterns reflect systematic biases in the operations of police assigned to the Narcotics Division. These and other such biases argue that we ought not to rely on indices of drug activity derived from arrest records.

DENEAU, G.A. The measurement of addiction potential by self-injection experiments in monkeys. Drug Abuse: Current Concepts and Research. Edited by W. Keup. Springfield, Illinois: Charles C. Thomas. 1972. Pp. 73-79.

To determine addictional potential, Rhesus monkeys were allowed to initiate and maintain intravenous self-administration of various drugs. The monkey's responses to centrally acting drugs were in most cases similar to those in man, with the exception of hallucinogens. It was concluded that the narcotic agents, short-acting sedatives, and stimulants would all have high abuse liability: However, it was also concluded that mescaline and LSD would not present serious abuse problems. Hence the procedure should not be used as the only basis for predicting abuse liability.

DENEAU, G.A. Use of the monkey colony in studies of tolerance and dependence. University of Michigan Medical Center Journal 36: 212-215 (1970)

DEWEY, W.L. Behavioral procedures: An overview. Narcotic Antagonists. Edited by M.C. Braude, L.S. Harris, E.L. May, J.P. Smith and J.E. Villarreal. Advances in Biochemical Pharmacology, Vol. 8. New York: Raven Press, 1973.

Operant behavior techniques can be used to obtain potency estimates, determine duration of action, and study the ability to produce tolerance and/or physical dependence of narcotic agonists or antagonists. These techniques can be used to differentiate between those narcotic antagonists producing positive and those producing negative reinforcing properties. Pentazocine, propiram fumarate, and cudeine show positive reinforcement properties whereas nalorphine and cyclazocine show negative reinforcement properties. A clear distinction is seen in the potency of narcotic antagonists to produce adverse effects in drug free as opposed to post dependent monkeys. Much less naloxone or nalorphine is required to produce apparently adverse effects in post dependent monkeys than in previously drug naive animals. The problem of adverse effects of narcotic antagonists in treatment of post-opiate, addicts may be mininized since tolerance appears to develop to many of the subjective effects of cyclazocine rather than to its antagonistic property. The narcotic antagonist analgesics cyclazocine, levallorphan, and pentazocine increased the response rates in an avoidance schedule and increased spontaneous activity while producing a decrease in rat whole brain norepinephrine levels. Naloxone did not block the effect of these drugs on locomotor activity or on the decrease in whole brain norepinephrine, but did antagonize their stimulatory effect on operant behavior. This suggests that only the stimulatory effect of these drugs on operant behavior was specific.

DEWEY, W.L. Narcotic-antagonist assay procedures in dogs. Narcotic Antagonists. Edited by M.C. Braude, L.S. Harris. E.L. May, J.P. Smith and J.E. Villarreal. Advances in Biochemical Pharmacology, Vol. 8. New York: Raven Press, 1973. Pp. 263-272.

Assays of antagonists against overt behavioral effects or respiratory depression produced by narcotic analgesics in dogs are useful in predicting narcotic antagonist activity in man. Anesthetized dogs have been used to test the ability of compounds to antagonize the respiratory depression produced by narcotic analgesics. There is correlation between the activity of antagonists in reversing respiratory depression caused by opiates in dogs and their potency in reversing many of the effects of opiates in man. Physical dependence on narcotic analgesics can be produced in dogs by a 1 day I.V. infusion of an opiate. This model can be used for studying addiction liability of an unknown compound or for the ability of pretreatment with an antagonist to inhibit dependence development. Though time consuming and expensive, dog assays are reproducible. However, quantification of dog responses has presented difficulties.

DIAB, I.M., FREEDMAN, D.X. and ROTH, L.J. /3H/ lysergic acid diethylamide: Cellular autoradiographic localization in rat brain. Science 173: 1022-1024 (September, 1971)

Intravenous administration of /3H/ lysergic acid diethylamide (LSD) to rats resulted in accumulation of the drug in the brain within 15 minutes. Autoradiographic methods were used to differentiate free and bound /3H/LSD in brain tissue. Free /3H/ LSD was generally distributed in the pituitary and pineal glands, cerebellium, hippocampus, and choroid plexus. Bound /3H/ LSD was localized in neurons of the cortex, caudate nucleus, midbrain, and medulla, as well as in choroid plexus epithelium.

DIAB, I.M. and ROTH, L.J. Cellular autoradiography of ^{3}H-LSD in brain, ^{3}H-thymidine in intestine, WR-2529-^{14}C in bone utilizing dry mounted, frozen, freeze-dried sections. Journal of Microscopy 96(Part 2): 155-164 (October, 1972)

An autoradiographic technique utilizing freeze-dried frozen sections dry mounted on dry photographic emulsion was used in conjunction with conventional histological tissue processing, i.e. fixed, dehydrated, cleared, embedded, de-embedded, and wet-mounted on photographic emulsion. to differentiate between the free and the bound form of the compounds. The freeze-dried frozen section method was extended to include undecalcified, unfixed, unembedded hardbone, cartilage and bone marrow with good histological details. The compounds utilized were ^{3}H-thymidine in the intestinal tissue and ^{3}H-LSD in brain tissue and the radio-protective agent WR-2529-^{14}C in bone. The localization of ^{3}H-LSD in the various regions of the brain are also described. Solid-liquid nitrogen slush -210°C, having increased temperature gradient and good thermal conductivity was used for freezing tissue samples without ice crystal formation or tissue destruction.

DOORENBOS, N.J., FETTERMAN, P.S., QUIMBY, M.W. and TURNER, C.E. Cultivation, extraction, and analysis of Cannabis sativa L. Annals of the New York Academy of Sciences 191: 3-14 (December. 1971)

DROPPLEMAN, L.F. and McNAIR, D.M. Screening for anticholinergic effects of atropine and chlordiazepoxide. Psychopharmacologia 12: 164-169 (1968)

Mild tranquilizers are suspected of having anticholinergic as well as anti-anxiety effects; if so, a reduction in palmar sweating in response to a tranquilizer cannot be interpreted simply as an anti-anxiety effect. A simple, reliable, and valid technique for measuring palmar sweating was used to compare the response curves of placebo; a known anti-cholinergic agent, atropine sulfate; and a mild tranquilizer, chlordiazepoxide, in a double-blind, balanced, repeated measures design. A significant atropine effect and reliable correlations with arousal were demonstrated, and no evidence of an anticholinergic effect of chlordiazepoxide was found within 90 min with the drug dosage used. Conditions are specified for the appropriate use of the FSP as a measure of the anti-anxiety effects of chlordiazepoxide.

DYKSTRA, L. and McMILLAN, D.E. Shock-intensity adjustment by squirrel monkeys under a titration procedure following administration of morphine, nalorphine, pentazocine, propoxyphene, delta-8-tetrahydrocannabinol (delta-8-THC) or chlorpromazine. Federation Proceedings 33: 516 (1974)

A titration procedure was used to determine the level at which squirrel monkeys would maintain an A.C. electric current applied continuously to their tails. Under the titration procedure the intensity of the electric shock increased by 0.25 milliamperes (mA) every 2 seconds to a maximum level of 8.00 mA. Each response on a lever by the monkeys reduced the shock intensity by 0.25 mA. Under control conditions the monkeys responded at a rate which maintained the shock intensity between 0 and 0.75 mA. Injections of morphine (1-4 mg/kg), nalorphine (5-30 mg/kg), pentazocine (3-17. 5 mg/kg), propoxyphene (3-100 mg/kg) delta-8-THC (5.6-15 mg/kg or chlorpromazine (0.3-3 mg/kg were given 30 minutes before some sessions. The monkeys adjusted the shock intensity to higher levels after morphine (2, 3 and 4 mg/kg), pentazocine (10 mg/kg), propoxyphene (56 mg/kg) and delta-8-THC (15 mg/kg). Increases in the shock intensity after morphine were much larger than increases obtained after administration of the other drugs. After nalorphene, the shock intensity was not adjusted to higher levels, although vomiting was observed after the higher doses. Chloropromazine either completely eliminated responding for long periods of time or had no effect.

EBBIGHAUSEN, W.O.R., MOWAT. J.H., STERNS, H. and VESTERGAARD, P. Mass fragmentography of morphine and 6-monoacetylmorphine in blood with a stable isotope internal standard. Biomedical Mass Spectrometry 345-354 (1974)

A mass fragmentographic method for the estimation of free and bound morphine and free 6-monoacetylmorphine in blood has been developed. It uses stable isotope internal standards and has a sensitivity of about 1 ng per ml or about 100 times better than ordinary gas chromatography. The focusing on specific high molecular fragments of the molecules gives high specificity to the assay and the stable isotope internal standards allow correction for losses occurring in the preparative steps of the analysis. A sensitive, specific method for monoacetylmorphine is particularly valuable since this compound seems to be a specific metabolite of heroin.

EBBIGHAUSEN, W.O.R., MOWAT. J.H., VESTERGAARD, P. and KLINE, N.S. Stable isotope method for the assay of codeine and morphine by gas chromatography-mass spectometry. A feasibility study. Advances in Biochemical Psychopharmacology, Vol. 7. New York: Raven Press, 1973. Pp. 135-146.

EICHBERG, R.H. and BENTLER, P.M. Current issues in the epidemiology of drug abuse as related to psychosocial studies of adolescent drug use. Presented at the National Institute on Drug Abuse Drug Lifestyles Conference, St. Simons, Georgia, January, 1975.

Developing a set of potentially heuristic items to predict drug use is discussed in terms of current issues in the epidemiology of drug abuse. The utility of predictive research is questioned in view of multi-dimensional complexities in the drug field. The problem areas of defining terms, deciding the type of predictions desired, selecting relevant target populations, being cognizant of fads, and keeping in mind a variety of data sources which might be necessary to complete a prediction equation are focused on. Demographic variables which are relevant to predicting drug use are briefly reviewed. Additionally, the nature of a possible collaborative research effort is evaluated in relation to the importance of interpreting data regarding trends and dynamics of the populations being studied.

ELLINWOOD, E.H., ASNIS, S.F., HAMMOND, W.E. and LLOYD, S.C. Drug abuse record keeping system with an interactive computer. I: Application. Presented at the 34th conference on Problems of Drug Dependence, Ann Arbor, Michigan, 1972.

ELLINWOOD, E. H., JR. and BALSTER, R. L. Rating the behavioral effects of amphetamine. European Journal of Pharmacology 28: 35-41 (1974)

A nine point rating scale with a highly standardized protocol for assessing the continuum behavioral effects of amphetamine (e.g. hyperactivity, stereotypy, dyskinetic-reactive effects) in rats is described. Dose-response curves for d- and l-amphetamine were obtained demonstrating a 4 : 1 potency ratio of d- to l-. The capability of the rating scale to assess antagonism of d-amphetamine by pimozide suggested that this scale may be a useful quantitative measure of neuroleptic activity of drugs.

FELDMAN. H. W. Street Status and the Drug Researcher: Issues in Participant-Observation. Washington, D.C.: The Drug Abuse Council, Inc., 1974.

FENIMORE, D.C. and DAVIS, C.M., JR. Rapid screening of urine for detection of narcotic drugs. Advances in Mental Science: Drug Dependence. Austin, Texas: University of Texas Press, 1970. Pp. 242-250.

FENIMORE, D.C., FREEMAN, R.R. and LOY, P.R. Determination of delta-g-tetrahydrocannabinol in blood by electron capture gas chromatography. Analytical Chemistry 45(14): 2331-2335 (December. 1973)

Electron capture gas chromatographic determination of delta-9-tetrahydrocannabinol (delta-9-THC) in blood serum is described. The compound is detected as the heptafluorobutyrate on a dual column-dual oven gas chromatograph utilizing a capillary column as the final resolving component. The limit of detection is below 100 pg per ml with excellent reproducibility using hexahydocannabinol as an internal standard. Blood serum concentrations in experimental animals injected with 0.1 mg/kg delta-9-THC were determined with levels below 1 ng/ml four hours after administration.

FENTIMAN, A.F., JR., FOLTZ, R.L. and KINZER, G.W. Identification of non-cannabinoid phenols in marihuana smoke condensate using chemical ionization mass spectrometry. Analytical Chemistry 45: 580 (March. 1973)

FETTERMAN, P.S., DOORENBOS, N.J., KEITH, E.S. and QUIMBY, M.W. A simple gas liquid chromatography procedure for determination of cannabinoidic acids in Cannabis sativa L. Experientia 27: 988-990 (1971)

FINK, M. Drugs, EEG and behavior. Chapter X of Drugs and the Brain. Edited by P. Black. Baltimore, Maryland: Johns Hopkins Press, 1969. Pp. 149-160.

FINK. M. EEG classification of psychoactive compounds in man: Review and theory of behavioral associations. Psychopharmacology: A Review of Progress, 1957-1967. Edited by D. Efron, J. Cole, J. Levine and J.R. Wilttenborn. Washington, D.C.: U.S. Government Printing Office, 1968. Pp. 497-507.

This review summarizes studies of the changes in the scalp recorded EEG in alert man following the administration of psychoactive drugs. Psychoactive drugs can be classified into four classes and five subclasses according to the associated EEG changes, despite problems of quantification of the EEG changes and of behavior and variations in dose of drugs, populations and recording methods.

The BEG classification shows interesting relations to the clinical applications of the drugs, and leads to the expression of a theory of the association of EEG changes and behavior.

Applications of this association in man is seen in the identification and classification of novel psychoactive compounds in the treatment of depression and psychosis and in the classification of hallucinogenic drugs.

FINK, M. Electroencephalograms, the mental state and psychoactive drugs. Pharmacology for Physicians 3(5): 1-5 (May, 1969)

FINK, M. The human electroencephalogram: Index of clinical activity of new psychoactive agents. Modern Problems of Pharmacopsychiatry 2: 106-110 (1969)

The EEG changes with thiothixene in man are increased theta activity (4. 0-7. 5 cps.), decreased variability of frequencies, and a decrease in fast activity (13. 5-27. 5 cps.). Of the psychoactive drugs, this pattern is most similar to the phenothiazine anti-psychotic drugs, and classifies thiothixene as an anti-psychotic agent.

The classification of psychoactive agents by EEG criteria depends upon EEG quantification by analog or digital computer methods, especially those that provide concurrent measurement of changes in frequencies, amplitude, variability and pattern.

Classification of psychoactive agents by EEG pattern changes in man provides a method for the identification of new psychoactive drugs in clinical psychopharmacology.

FINK, M. Quantitative EEG classification of psychoactive drugs in man. The Nature of Sleep: Proceedings. Edited by U.J. Jovanovic. New York: International Publications Service, 1973. Pp. 76-78.

FINK, M. and ITIL, T. M. EEG and human psychopharmacology. IV: Clinical anti-depressants. Psychopharmacology: A Review of Progress, 1957-1967. Edited by D. Efron, J. Cole, J. Levine and J.R. Wittenborn. Washington, D.C.: U.S. Government Printing Office, 1968. Pp. 671-682.

Recent studies define direct associations between the clinical activity and the EEG signatures of psychoactive compounds in man. Among the defined patterns, the induction of beta and theta activities increased variability of frequencies and reduction in alpha activity characterize two active tricyclic anti-depressants, imipramine and amitriptyline, and some anticholinergic drugs, as Ditran and atropine.

The EEG patterns of the benzomorphan analgesic and narcotic anatagonist cyclazocine, are similar to those of imipramine.

Two open clinical studies of cyclazocine in depressed psychotic subjects demonstrate clinical anti-depressant activity similar in degree to imipramine.

The use of EEG in the identification and classification of clinically active anti-depressants is suggested.

FINK, M., ITIL, T. and SHAPIRO, D. Digital computer analysis of the human EEG in psychiatric research. Comprehensive Psychiatry 8: 521-538 (1967)

FINK, M. and SHAPIRO, D.M. EEG indices of CNS bioavailability of psychoactive drugs. Electroencephalography and Clinical Neurophysiology 33: 246-247 (1972)

Previously, we examined the EEG literature and defined the types of EEG changes with known psychoactive drugs. These profiles have been used to classify new experimental drugs, and to develop time and dose response curves. In earlier studies we defined the antidepressant qualities of cyclazocine. the mixed antidepressant antianxiety qualities of doxepin, and the sedative qualities of fenfluramine, demonstrating a utility of the EEG classification for new drug identification (Ann. Rev. Pharmacol., 1969, 9:241)

In defining time and dose relationships, these methods were first used to distinguish two oral doses of amobarbital. 50 and 100 mg, from a 300 mg sustained release formulation: and again to distinguish oral amobarbital, 50 and 100 mg from dextroamphetamine (10 mg) and fenfluramine (40 mg). We have also applied the technique to two formulation questions as measures of bioavailability in the CNS: a comparison of oral thiothixene in concentrate and capsule forms; and two formulations of doxepin from different manufacturers.

These studies are done in male volunteers, using digital period analysis, 320 sps. 20 sec epochs, and a continuous alerting task. The effects of each drug dose and formulation are compared to placebo for each of 20 measured variables, using linear regression data reduction.

The data of two studies, thiothixene and doxepin, will be used to exemplify the present state of this method as an index of drug bioavailability.

FINK, M. and SHAPIRO, D.M. EEG patterns as an index of clinical activity of psychoactive drugs. Electroencephalography and Clinical Neurophysiology 27: 710 (1969)

The human scalp record of cerebral electrical activity is easily recorded, sensitive to drug effects and related to clinical behavior. Frequency analysis, amplitude integration, averaged evoked response, activated EEG to barbiturates and chloralose, and changes during all night sleep recording are among the many methods of analysis that have been investigated.

Fink, M. and Shapiro, D. M. EEG patterns . . . continued

In a review of the effects of psychoactive drugs in man a classification of drugs emerges which is related to the clinical efficacy of the compounds. This classification is being applied to the identification of the clinical effects of new, potentially psychoactive compounds.

1. The EEG pattern of cyclazocine is similar to that of imipramine, and in clinical trials it was found to be an active antidepressant.

2. The EEG patterns of thiothixene and trifluperidol are similar to chlorpromazine. The psychoactive range is in the same class.

3. The EEG patterns of fenfluramine. an anorexigenic compound, are most like 50 mg amobarbital and differ from dextroamphetamine. In clinical trials, the principal secondary effects have been sedation and drowsiness.

4. Time-dose studies of 50 mg and 100 mg amobarbital and 300 mg sustained release amobarbital showed different patterns for the different drug forms.

5. The separation of sympathomimetic and anticholinergic hallucinogens by EEG criteria provides a basis for the selection of appropriate antagonists.

Quantitative EEG provides a useful means of identifying and classifying psychoactive drugs in man for therapeutic purposes.

FINK, M. and SHAPIRO, D.M. EEG-profile for psychopharmacology: A progress report. Electroencephalography and Clinical Neurophysiology 31: 103-106 (1971)

Since the mid-1950's. quantitative studies of EEG changes with psychoactive drugs demonstrate intimate relationship between changes in the human scalp EEG and the behavioral effects of psychoactive drugs. A review of the literature of drug effects on EEG in alert man yielded a useful classification of psychoactive drugs (Ann. Rev. Pharmacol. 1969, 9: 241). This scheme classifies known psychoactive drugs into clinically similar clusters.

Using period analysis, digital processing (320 sps, 20-60 sec epochs) with an IBM 1800 process control system, we have defined EEG profiles of new compounds, fenfluramine and doxepin, and compared these to the EEG profiles of amobarbital, dextroamphetamine, diazepam and imipramine, used as standards.

Fenfluramine exhibited a profile highly correlated with that of amobarbital and doxepin exhibited an EEG profile most like imipramine (1 1 measures) with some similarities to diazepam (4 measures) - both EEG classifications closely related with their clinical activity.

Bioavailability studies demonstrated equivalent EEG profiles for two formulations of doxepin; and for two formulations of thiothixene, one capsule and one liquid concentrate. In the thiothixene study the profiles were identical, but the onset was 12-15 min earlier for the concentrate.

Profile studies have also been done with new compounds before clinical trial, and the EEG profiles utilized in identification of target populations and symptoms.

These data extend the classification model and support a theory of association of EEG and behavior with psychoactive drugs.

FISHMAN. J., COTTER, M.L. and NORTON, B.I. Narcotic antagonists. 2. Preparation and biological stability of naxolone-7, 8-^{3}H. Journal of Medicinal Chemistry 16: 556-557 (1973)

FISHMAN, J. NORTON, B.I., COTTER, M.L. and HAHN, E.F. Preparation of morphine-6-^{3}H and its isotopic stability in man and in rat. Journal of Medicinal Chemistry 17(7): 778-781 (1974)

FISHMAN, J., NORTON, B.I. and HAHN, E. Differential distribution of opiate agonists and antagonists in the rat brain as determined by double isotope techniques. Presented at Meeting of the American Society of Biological Chemists, 1974.

The simultaneous or sequential administration of an opiate agonist and antagonist labelled with different isotopes allows for the precise determination of their relative concentrations in specific areas of the CNS. Disproportionately greater antagonist to agonist concentration ratios in specific CNS sites could be indicative of opiate receptor presence and allow its localization under physiological conditions. Male rats were injected with morphine-N-$^{14}CH_3$ and simultaneously or 15 and 25 minutes later with naloxone-7, 8^{3}H. All animals were sacrificed 30 minutes after the morphine injection and the ^{3}H and ^{14}C content of various tissues was obtained after combustion in a tissue oxidizer. The ^{3}H to ^{14}C ratio in the brain was 7 times greater than in the blood. Within the brain the medial thalamus exhibited significantly greater ^{3}H to ^{14}C ratios than other CNS sites reflecting relatively greater naloxone and diminished morphine uptake. Reversal of isotopic markers by using morphine-6^{3}H and naloxone-N-^{14}C-allyl did not alter these results indicating that N-demethylation was not responsible for the observed disproportionation. The foregoing data is consistent with the localization of opiate receptors in the medial thalamus of the rat brain.

FISHMAN, J., NORTON, B.I. and HEMBREE, W. Preparation of morphine-^{3}H by microwave discharge activation of tritium gas. Journal of Labelled Compounds 9(3): 563-565 (July-September, 1973)

FISHMAN, J., ROFFWARG, H. and HELLMAN, L. Disposition of naloxone-7, 8-^{3}H in normal and narcotic-dependent men. The Journal of Pharmacology and Experimental Therapeutics 187(3): 575-580 (1973)

Naloxone-7, 8-^{3}H was administered intravenously and orally on separate occasions to the same normal male subject and its disposition was examined. The fate of intravenous naloxone-7, 8-^{3}H was also studied in an opiate-dependent subject both while on heroin maintenance and after withdrawal. In all cases the urinary excretion was rapid but incomplete, never exceeding 70% of the dose over 72 hours. Initial plasma concentrations of naloxone were low with a rapid rate of disappearance. Oral naloxone entered plasma quickly but in a metabolized form. The volume of distribution, plasma half-life and metabolic clearance rate of naloxone as calculated from the intravenous studies were about 200 liters, 90 minutes and 2500 liters/day, respectively.

FORREST, F.M. and FORREST, I.S. Piperacetazine in chronic mental patients: Clinical observations and new urine color test. Current Therapeutic Research 14(11): 689-695 (November, 1972)

Piperacetazine in daily doses of 25 to 150 mg. was administered to 22 male patients with chronic mental illness for periods of six weeks to 15 months. Maximum improvement occurred in the dosage range of 30 to 75 mg. per day. Infrequent side effects (insomnia and akathisia) were dose-related. Three patients (14%) improved beyond the level reached by previous chemotherapy and were discharged from the hospital. Seven patients (32%) showed marked or moderate improvement. Six patients (27%) were unchanged, while six patients (27%) were rated worse.

A rapid urine color test for direct semi-quantitative determinations of excreted piperacetazine was developed for three dosage levels.

FORREST, I.S., BROOKES, L.G. and BARTH, R. Use of hepatic microsomes in the preparation of model drug metabolites. Proceedings of the Western Pharmacological Society 13: 1-4 (1970)

FORREST, I.S., FORREST, F.M., BOLT, A.G. and SERRA, M.T. An attempt to correlate urinary chlorpromazine excretion with clinical response to drug therapy. Proceedings of the 5th International Congress on Neuro-Psycho-Pharmacology. Amsterdam, the Netherlands: Excerpta Medica Foundation, 1967. P. 1186.

FORREST, I.S., GREEN, D.E. and SERRA, M.T. The use of XAD-2 nonionic polymeric adsorbent in the analysis of chlorpromazine and its metabolites. Psychopharmacology Bulletin 9(2): 20-21 (1973)

FORREST, I.S., GREEN, D.E. and WURSCH. ^{3}H-delta-9-tetrahydrocannabinol (THC) metabolites in rhesus monkey urine: Efficient new extraction procedures and implications for metabolite structures. Abstracts of Volunteer Papers. Fifth International Congress on Pharmacology, San Francisco, California, July, 1972.

FORREST, I.S., ROSE, S.D., BROOKES, L.G., HALPERN, B., BACON, V.A. and SILBERG, I.A. Fluorescent labeling of psychoactive drugs. Agressologie 11: 127-133 (1970)

Fluorescent derivatives of demethylated or hydroxylated metabolites of the psychoactive drugs chlorpromazine, imipramine and amitlptyline have been prepared by "dansylation". These compounds have been characterized by thin layer chromatograph spectro photofluorometry and mass spectrometry. They will serve as reference compounds for identification and assay of biotransformation products of these drugs in biological material from patients and experimental animals.

FRACCHIA. J. F., FIORENTINO. D., SHEPPARD, C. and MERLIS, S. A comparison of techniques for the scoring of avoidable errors on the Raven Progressive Matrices. Journal of Psychology 72: 93-98 (1969)

The Raven Progressive Matrices of 88 narcotic users, divided into four MMPI profile pattern groups, were scored for avoidable errors with the use of three scoring methods. Two of the methods defining avoidable errors in terms of empirically determined item-difficulty levels indicated significantly more reasoning errors were made by patients with paranoid profiles than by patients with either primary or secondary sociopathic patterns. The third method, based upon expected set scores, did not score significantly different numbers of avoidable errors in the four groups. The data were interpreted as indicating that the manner of defining and that of scoring RPM avoidable errors are important factors in determining sensitivity to reasoning errors related to pathological ideation. It was suggested that where mental illness affects consistency of performance, appropriately defined and objectively scored avoidable error measures can be used to assess the impairment of intellectual functioning.

FRACCHIA, J., FIORENTINO, D., SHEPPARD, C. and MERLIS, S. Raven Progressive Matrices avoidable errors as a measure of psychopathological ideational influences upon reasoning ability. Psychological Reports 26: 359-362 (1970)

The Raven Progressive Matrices protocols of 88 narcotic addicts, divided into four MMPI profile pattern groups, were scored for avoidable errors. Ss having psychotic-like profiles (428' and 987') made significantly more avoidable reasoning errors than Ss with sociopathic patterns (42' and 49'). These data were interpreted as evidence of the sensitivity of avoidable error measures to disturbances in consistency and accuracy of comparative and analogical reasoning performance. It was suggested that avoidable error indices might be used to (a) judge the effects of pathological ideation upon complex reasoning, (b) estimate potential level of intellectual functioning in clinical populations, and (c) serve as a criterion for treatment efficacies.

FRIEDHOFF. A.J. Co-crystallization analysis: A short method for identification and quantitative determination of DMPEA and other biological compounds. Biological Psychiatry 5(2): 199-206 (1972)

A rapid quantitative method was developed for the determination and identification of dimethoxyphenethylamine (DMPEA) or any compound, which can be acetylated, or otherwise coupled with a radioactive compound to form a crystalline labelled derivative. Material in extracts of biological tissues or fluids is subjected to acetylation with ^{14}-C-acetic anhydride. The unlabelled acetyl derivative of the compound to be assayed is added to the mixture of acetylated material as a carrier, and repeated fast "forced out" co-precipitations are carried out followed by several normal crystallizations. A weighed portion of the crystals are then subjected to two-dimensional chromatography and radioactivity on one appropriate area of the chromatogram is determined. From the specific activity of the final carrier crystals, the quantity of the compound being assayed can be determined. This method should make it possible to obtain proof of identity and carry out quantitative analysis of many compounds that were difficult or impossible to assay by previous methods.

FRIEDHOFF, A.J., SCHWEITZER, J.W. and MILLER, J. Biosynthesis of mescaline and N-acetylmescaline by mammalian liver. Nature 237: 454-455 (June, 1972)

GARRETT, E.R., BRES, J., SCHNELLE, K. and ROLF, L.L., JR. Pharmacokinetics of saturably metabolized amobarbital. Journal of Pharmacokinetics and Biopharmaceutics 2(1): 43-103 (1974)

The pharmacokinetics of intravenously administered amobarbital (5-40 mg/kg) and its major metabolite, hydroxyamobarbital, were evaluated by GLC monitoring in the blood and urine of dogs. The induction of alkalosis and acidosis by adjustment cf respiration rates and by modification of blood pH showed relatively instantaneous and significant changes in apparent blood levels of the amobarbital that could be assigned to variable ratios of ionized to un-ionized drug, with the latter showing greater partition into peripheral tissues, i.e., an effective change in apparent volumes of distribution. It was demonstrated that metabolism of amobarbital was a saturable process and largely zero order over the entire dose ranges studied. The rate of appearance of hydroxyamobarbital was of the same magnitude for the various doses. Enzymic induction by prior chronic administration of phenobarbital dramatically increased the rate of metabolism, and the operational pharmacokinetic model was consistent with the two-compartment open body model with first-order transferences. This model also held at all times for intravenously administered hydroxyamobarbital. The administration of SKF 525 greatly inhibited the rate of amobarbital metabolism in the dog.

GARRETT, E.R. and HUNT, C.A. Physicochemical properties, solubility, and protein binding of delta-9-tetrahydrocannabinol. Journal of Pharmaceutical Sciences 63(7): 1056 -1064 (July, 1974)

The rate and extent of glass binding of delta-9-tetrahydrocannabinol in aqueous solution depend on the surface area and pretreatment of glass and the concentration of the drug. A total of 20 and 40% at 0.1 and 0. 05 mu-g/ml, respectively, was bound to 50-ml volumetric flasks but could be minimized by silyl pretreatment of the glass. The drug rapidly diffused into plastics, and 70-97% was taken up by the rubber closures used for plasma vials. These bindings precluded classical methods of solubility determination, so spectral and particle-size counting determinations, which observed those concentrations at which true solution was terminated, were used. The aqueous solubility was a linear function of both the ethanol concentration (increasing) at constant ionic strength and the square root of the ionic strength (decreasing) at constant ethanol concentration. The salting-out coefficient was of high magnitude and typical solubilities were 2.8 mg/liter in water and 0.77 mg/liter in 0.15 M NaCl at 23°. The bindings also precluded the use of the classical methods of equilibrium dialysis and ultrafiltration to determine the protein binding of tetrahydrocannabinol. A method of variable plasma concentrations was devised, so protein binding was determined from the pseudoplasma concentrations of the drug after the separation of the pseudoplasma from the red blood cells added to form pseudoblood with known concentrations of delta-9-tetrahydrocannabinol. This use of the competition between the high partitioning of drug between red blood cells with plasma water (H)= 12. 5) and the binding to plasma protein permitted an estimate of 97% binding which was not drug concentration dependent. The spectrophotometric pKa of delta-9-tetrahydrocannabinol was 10. 6.

Garrett, E.R. and Hunt, C.A. Physicochemical properties . . . continued
Delta-9-tetrahydrocannabinol degraded readily in acid solutions. Subsequent to a rapid loss, the kinetics appeared to be first-order and specific hydrogen-ion catalyzed. Concomitantly, small amounts of delta-8-tetrahydrocannabinol were were produced, as were two GLC observable products, P_2 and P_3, and the rate of their appearance appeared to parallel the rate of delta-9-tetrahydrocannabinol degradation. A peak, P_1, also appeared almost instantaneously but did not parallel drug degradation.

GARRETT, E.R. and HUNT, C.A. Picogram analysis of tetrahydrocannabinol and application to biological fluids. Journal of Pharmaceutical Sciences 62(7): 1211-1214 (July, 1973)

GARRETT, E.R. and TSAU, J. Stability of tetrahydrocannabinols I. Journal of Pharmaceutical Sciences 63(10): 1563-1574 (October, 1974)

Delta-9-tetrahydrocannabinol, as monitored by flame-ionization GLC at various temperatures, degrades by a biphasic semi-logarithmic curve with time in acidic aqueous solution (less than 1 mg/liter) below pH 4 to GLC-observable products with separate retention times and the degradations are specific hydrogen-ion catalyzed. The products are considered as delta-8-tetrahydrocannabinol, P_1, P_2 and P_3 and can be observed and isolated by TLC. These products do not appear above pH4 in the neutral region, and these degradations are primarily first order, are not biphasic, and are pH independent. The half-life of delta-g-tetrahydrocannabinol is about 15 min at 37° and pH 1, typical stomach conditions. The product P_1 may give rise to cannabinol by the GLC and TLC procedures since the IR, UV, TLC, NMR, and GLC of thin-layer chromatographed P_1 and cannabinol are coincident, but chloroform extracts do not show the higher absorbances expected if the product that forms in solution to give P_1 is cannabinol. The products P_2 and P_3, isolated by TLC, are consistent with the expected properties of delta-9-hydroxycannabidiol and 9-hydroxycannabinol, respectively, by IR, UV, NMR, and mass spectroscopy. The final amounts of delta-8-tetrahydrocannabinol, P_1, P_2 and P_3 are in a constant ratio independent of pH below pH 4. Delta-9-tetrahydrocannabinol, as monitored by flame-ionization GLC, degrades solely by a first-order process to an equilibrium with P_2 and P_3 at acidic pH values and the process is specific hydrogen-ion catalyzed. The equilibrium appears to be independent of pH below pH 4 and is the same when TLC-isolated P_2 or P_3 is used as the starting material. It follows that the acidcatalyzed isolated double-bond migration favors delta-8-tetrahydrocannabinol over the delta-9 compound, and it is most probable that the equilibrating P_2 and P_3 are results of water addition to the isolated double bond and ether solvolysis. The product that gives rise to the P_1 retention time that ultimately gives cannabinol is structurally indeterminate at present.

GAZTANAGA, P., ABRAMS, R., SIMEON, J., JONES, T. and FINK, M. Clinical evaluation of GP-41299: An antianxiety agent of the doxepin type. Arzneimittel-Forschung 22: 1903-1905 (1972)

GERSHMAN, H., POWERS, E., LEVINE, L. and VANVUNAKIS, H. Radioimmunoassay of prostaglandins, angiotensin, digoxin, morphine and adenosine-3-5-monophosphare with nitrocellulose membranes. Prostaglandins (in press)

GESSNER, P. K. The isobolographic method applied to drug interactions. Drug Interactions. Edited by P.L. Morselli and S.N. Cohen. New York: Raven Press, 1974. Pp. 349-362.

GOLDSTEIN, A. Accurate measurement of urinary morphine. New England Journal of Medicine 286: 1417 (1972)

GOLDSTEIN, A. Partial purification of an opiate receptor from mouse brain. Science 183: 749-753 (1974)

GOLDSTEIN, A., LOWNEY, L.I. and PAL, B.K. Stereospecific and nonspecific interactions of the morphine congener levorphanol in subcellular fractions of mouse brain. Proceedings of the National Academy of Sciences 68(8): 1742-1747 (August, 1971)

A method is described for analyzing the association of the opiate narcotic levorphanol with brain tissue into three components: nonsaturable, saturable nonspecific, and saturable stereospecific. The method may be of general applicability for the study of the interaction of drugs with body tissues. In mouse brain the stereospecific binding of levorphanol represents only 2% of the total association of drug with tissue, and it was found only in certain membrane fractions. The material responsible for the stereospecific binding might be the opiate receptor.

GOLDSTEIN, J.W. Assessing the interpersonal determinants of adolescent drug use. Presented at the National Institute on Drug Abuse Conference on Drug Lifestyles, St. Simons, Georgia, January, 1975.

The nature of items on model surveys of adolescent drug usage is discussed in the framework of a person-situation interactionist view of use causation. If drug effects are dependent upon the setting of use, then an assessment of the social norms of the respondent's salient reference groups should be valuable. Usage conceptualized as a dynamic pattern of a range of drugs and viewed according to the role which it plays in the life of the user will be most meaningful. A changing world means that assessments of usage must be periodically reconceptualized.

CORODETZKY, C.W. Efficiency and sensitivity of two common screening methods for detecting morphine in urine. Clinical Chemistry 19(7): 753-755 (1973)

Modified procedures are described for extracting morphine from urine with organic solvents and with paper impregnated with ion-exchange resin, followed by detection by thin-layer chromatography. I propose that efficiency of extraction (percent recovery) be defined in terms of the amount of drug reaching the detection system vs. the amount in the total urine sample analyzed. Percent recoveries were determined experimentally with 95% confidence limits and 95%, P = .05 tolerance limits, and were 60.6% for the organic solvent procedure and 48.2% for the ion-exchange paper procedure. Sensitivity of the overall detection method can be defined as the concentration of drug in the urine detectable at least 99% of the time. Values (95% confidence limits) determined experimentally were 0.19 (0.14-0.25) mu-g/ml for the organic solvent procedure and 0.16 (0.07-0.35) mu-g/ml for the ion-exchange paper procedure.

GORODETZKY, C.W. Sensitivity of thin-layer chromatography for detection of 16 opioids, cocaine and quinine. Toxicology and Applied Pharmacology 23: 511-518 (1972)

A method has been developed to evaluate quantitatively the sensitivity of thin-layer chromatography (TLC). For each drug studied, seven different amounts of the drug and a solvent control are randomly spotted across a 20 x 20 cm thin-layer plate. Ten to 30 such plates are made with the technician blind to the order of spotting. For each amount of drug, the ratio of (number of spots detected)/(number of spots plated) is determined, converted to percentage and plotted on log probability paper. The method of Litchfield and Wilcoxon is used to determine the amount which can be identified any given percentage of the time (termed the "identifiable amount" or IA) and its 95% confidence limits. Sensitivity data for 16 opioids, cocaine and quinine, using iodoplatinate alone and followed by ammoniacal $AgNO_3$ and $KMnO_4$ for spot detection show that TLC is not uniformly sensitive for the detection of all opioids. Adding $AgNO_3$ and $KMnO_4$ after iodoplatinate produced an increase in sensitivity, with the exception of the arylpiperidines studied, levallorphan, propoxyphene, cocaine and quinine. A relative detection index for each drug, taking into account sensitivity for detection by TLC, euphorogenic dose and 24 hr urinary excretion relative to morphine showed that all opioids would not be predicted to be equally detectable in the urine following administration of equieuphorogenic doses. R_f data show widely overlapping tolerance limits between drugs, indicating that the R_f of a single unknown spot would be expected to be a poor measure of specificity under these TLC conditions.

GORODETZKY, C.W., ANGEL, C.R., BEACH, D.J., CATLIN, D.H. and YEH, S.Y. Validity of screening methods for drugs of abuse in biological fluids. I. Heroin. Clinical Pharmacology and Therapeutics 15(5): 461-471 (May, 1974)

In evaluating methods of detecting drugs of abuse in biological fluids it is of special importance to determine the ability of detecting a drug or its metabolites in biological fluids. To evaluate several methods of detecting heroin use by urine analysis for morphine and its metabolites, single intravenous doses of 2. 5 and 5 mg/70 kg heroin were administered a week apart in random order to 10 nontolerant subjects and their urine was collected for the week following. Along with pre-drug control urines, each sample was coded, randomized, and analyzed under blind conditions by the following methods: (1) thin-layer chromatography (TLC) with iodoplatinate preceded by each of 4 extraction procedures, organic solvent and ion exchange resin impregnated paper extraction both without and with prior acid hydrolysis; (2) the free radical assay technique (FRAT); (3) radioimmunoassay (RIA); and (4) the Technicon Autoanalyzer. There was a high probability of detection for the first 8 hours by all methods except the Technicon Autoanalyzer (which gave a low proportion of positives 8 hours after the 2.5 mg per 70 kg heroin dose); up to 16 hours with TLC procedures with hydrolysis and FRAT; and up to 32 to 48 hours with RIA.

GORODETZKY, C.W. and KULLBERG, M.P. Validity of screening methods for drugs of abuse in biological fluids. II. Heroin in plasma and saliva. Clinical Pharmacology and Therapeutics 15(6): 579-587 (June, 1974)

Five subjects received 3 single intravenous doses of heroin, 2.5, 5, and 10 mg per 70 kg and 1 oral dose of dextromethorphan, 60 mg per 70 kg; another 4 subjects received morphine, 30 mg, subcutaneously, 4 times per day for 3 months. Saliva and plasma samples were collected at intervals for 48 hours following each single drug dose and hourly for 6 hours between chronic doses. Plasma samples were analyzed for opiate by RIA, and saliva samples by RIA, a modified FRAT, and the EMIT. The low dose of heroin was not consistently detectable at any sampling time in either the plasma or the saliva. The medium and high doses were detectable with high probability for 2 to 4 hours in plasma and 1 to 2 hours in saliva. Dextromethorphan was not detectable in plasma but was detected with high probability in saliva for 30 minutes by EMIT and 2 hours by FRAT. During chronic administration there were high probabilities of detection of morphine in plasma for at least 6 hours and in saliva for 3 to 4 hours after the last morphine dose. While these fluids do not appear to be as useful as urine in routine screening for heroin, they may be useful in the detection of high-dose chronic abuse.

GREEN, D.E. Automated detection of abused drugs by direct mass fragmentography. Proceedings of the Western Pharmacological Society 15: 74-77 (1972)

GREEN, D.E. Direct, multiple ion detection of chlorpromazine by mass fragmentography. The Phenothiazines and Structurally Related Drugs. Edited by I.S. Forrest, C. J. Carr and E. Usdin. New York: Raven Press, 1974.

Automated specific molecule detection by means of multiple-ion detection mass fragmentography using a specifically designed dedicated microcomputer to control the operation of, and to retrieve and analyze the data from, a unique mass-analyzer system is described. Utilization of this powerful new tool for the study of drug disposition in a somewhat conventional manner in conjunction with a gas chromatograph is described.

Examples of direct mass fragmentography (i.e., without the use of a gas chromatograph) demonstrate the ability of this novel system to detect and quantitate chlorpromazine and its metabolites at levels from 10 ng to 10 mu-g in a few seconds in complex biological specimens.

GREEN, D.E. and FORREST, I.S. Fully automated detection and assay of drugs by "direct multiple-mass fragmentography," a new, ultra-sensitive analytical technique. Abstracts of Volunteer Papers. Fifth International Congress on Pharmacology, San Francisco, California, July, 1972. P. 88.

GREEN, D.E. and LITTLEJOHN, D.P. Automated analysis of biological specimens using a compound-specific detector. Proceedings of the Western Pharmacological Society 16: 226-230 (1973)

GREEN, D.E., ROSE, S.L. and FORREST, I.S. New Methodology for the detection and characterization of drugs and drug metabolites. Proceedings of the Western Pharmacological Society 14: 187-189 (1971)

GROSS, S.J., SOARES, J.R., WONG, S-L.R. and SCHUSTER, R.E. Marihuana metabolites measured by a radioimmune technique. Nature (in press)

HAMILTON, H.E., WALLACE, J.E. and BLUM, K. Improved methods for quantitative determination of methadone. Journal of Pharmaceutical Sciences 63(5): 741-745 (May, 1974)

A spectrophotometric method is described that permits the rapid analysis of methadone in urine or tissues at concentrations corresponding to therapeutic, maintenance, or toxic doses of that drug. As little as 5 mu-g may be detected in a biological specimen. The procedure involves an alkaline extraction into n-hexane and subsequent back-extraction into a ceric sulfate-sulfuric acid solution. The acid extract is refluxed with n-heptane for 30 min. oxidizing methadone to benzophenone which, in contrast to the unchanged drug, has a high molar absorptivity in the UV region. A GLC method is also described. Both procedures require fewer manipulations and less analysis time than previously reported methods for determining methadone.

HARRISON, S.D., JR., CHIU, P. and MAICKEL, R.P. Polyamide thin-layer chromatographic separation of DOPA metabolites and related compounds. Journal of Chromatography 85: 151-153 (1973)

The use of L-DOPA in therapy of Parkinsonism has stimulated interest in the metabolism of this compound in normal and pathologic states. Goodall and Alton separated 35 DOPA metabolites from the urine of healthy subjects by GLC. Seventeen of these metabolites, including 11 acidic compounds, were unidentified. Recently, 3-hydroxyphenylacetic acid, 3-methoxy-4-hydroxyphenyllactic acid, and 4-hydroxyphenyllactic acid were identified in the urine of patients receiving large oral doses of L-DOPA. More recently, 3-hydroxyphenylacetic acid has been shown to be produced from DOPA by the intestinal microflora. The substituted phenyllactic acids are products of a transamination pathway of metabolism enhanced by large doses of L-DOPA. This pathway, a major route for the metabolism of L-3-O-methylDOPA, as well as other possible pathways, may have significance in Parkinson patients, The production of 3-methoxy-4-hydroxyphenyllactic acid by such patients receiving L-DOPA confirms earlier observations of this metabolite in the urine of patients with DOPA-secreting tumors. The present study was prompted by the possibility that important DOPA metabolites may not yet have been identified and by the lack of a simple, readily-available method for the separation of potential DOPA metabolites differing only slightly in structure.

The advantages of polyamide thin layers for the separation of phenolic compounds has been recognized. This report includes TLC data obtained with authentic samples of compounds not previously available for study.

HARVEY, J.A. Physiological and pharmacological analysis of behavior. Advances in Behavioral Biology. Edited by R. Whalen. New York: Plenum Press, 1974. Pp. 125-147.

Recent developments in neuropharmacology, neurochemistry and neuroanatomy provide the contemporary student of brain function with a variety of techniques and thus the ability to perform manipulations and measurements not previously possible. In addition, we now know that brain lesions, stimulation or drugs produce effects on behavior that are mediated via changes in the functional amounts of putative synaptic transmitters that are localized within defined anatomical systems. It is no longer desirable, therefore, to employ a single technique in the biological analysis of behavior. Rather, we have the possibility of a unitary view concerning the mechanism by which a variety of methods affect behavior and an ability to relate behavior to anatomy, neurochemistry, and physiology.

HO, I.K., SUTHERLAND, V.C. and LOH, H.H. A model for the rapid development of tolerance to barbiturates. Research Communications in Chemical Pathology and Pharmacology 6(1): 33-46 (July, 1973)

The subcutaneous implantation of pellets of sodium pentobarbital (5.4 mg) in the back of a conscious mouse results in a measurable tolerance within 24 to 48 hours. The development and the degree of tolerance induced by pellet implantation were compared with mice receiving daily intraperitoneal injections of anesthetic doses of 75 mg or 100 mg/kg of sodium pentobarbital. An increasing number of mice failed to lose their righting reflex following each daily implantation and the reduction in sleep time in those that did was 58 percent following the second pellet at 48 hours and 73 percent following the third pellet at 72 hours. The percent reduction of sleeping time or degrees of tolerance in response to single challenge doses of either 75 mg or 100 mg/kg, i.p., of sodium pentobarbital in implanted mice were 65 percent (75 mg) or 68 percent (100 mg) by 24 hours (first pellet), 72 percent for both doses after 48 hours (second pellet), and 76 percent (75 mg) or 73 percent (100 mg) after 72 hours (third pellet). These percentages represent a significantly greater reduction in sleep time than the maximum 41 percent reduction produced on the fourth day of daily injections for 10 days of 75 mg/kg or the 40 percent reduction of sleep time in mice on the third day of five daily doses of 200 mg/kg of sodium pentobarbital. In addition, there was a reduced mortality rate in repeated pellet implantation as compared to daily injections of 100 mg/kg.

HO, I.K., YAMA MOTO, I. and LOH, H.H. A model for the rapid development of dispositional and functional tolerance to barbiturates. European Journal of Pharmacology (in press)

The subcutaneous implantation of a 75 mg pentobarbital pellet in the back of a conscious mouse resulted in a much more rapid development of tolerance to barbiturates than that produced in mice receiving daily intraperitoneal injections of 75 mg/kg sodium pentobarbital. Acceleration in tolerance development by pentobarbital pellet implantation was evidenced by a decrease in sleeping time after the challenge with either sodium pentobarbital or sodium barbital. The degree of hepatic microsomal drug enzyme induction after pentobarbital pellet implantation also was found to be significantly higher than that produced by the injection technique. Further studies demonstrated that the threshold for pentylenetetrazol-induced seizures was significantly reduced compared to that of the sodium pentobarbital daily-injected and control groups. These studies provide an animal model for studying the mechanism of barbiturate tolerance and dependence.

HOLDEN, J.M., ITIL, T., SIMEON, J. and FINK, M. Clinical laboratory test standards in new drug trials. Journal of Clinical Pharmacology and New Drugs 7: 1-8 (1967)

HOLLANDER, C. editor. Collection of Background Papers on Student Drug Involvement. Washington, D.C.: United States National Student Association, 1967.

HOLTZMAN, S.G. and JEWETT. R.E. Shock intensity as a determinant of the behavioral effects of morphine in the rat. Life Sciences 11 (Part I): 1085-1091 (September, 1972)

When a relatively high shock intensity is the reinforcer, morphine produces a well-defined dose-related increase in the rate of avoidance responding in the rat. This is in contrast to the usual depression of behavior associated with morphine administration. Thus, the qualitative nature of morphine's effects on behavior can be a function of environmental determinants. This type of procedure may be of value for studying certain aspects of the stimulant component of morphine's action.

HUANG, J.C-Y. and BADEN, M.M. Rapid methods of screening micro-quantities of abuse drugs from urine samples for microcrystal tests. Clinical Toxicology 6(3): 325-350 (1973)

A simple, comprehensive and economic system for detection of narcotic drugs is described. It provides a rapid method for screening microquantities of abused drugs from urine samples for microcrystal tests. The procedures and methods are presented.

HUGHES, J., KOSTERLITZ, H.W. and LESLIE, F.M. Assessment of the agonist and antagonist activities of narcotic analgesic activities of narcotic analgesic drugs by means of the mouse vas deferens. British Journal of Pharmacology 51: 139-140 (1974)

HUNT, H.F. Unconditioned stimulus functions of drugs: Interpretations, I. Chapter 5 of Stimulus Properties of Drugs. Edited by T. Thompson and R. Pickens. New York: Appleton-Century-Crofts, 1971.

ITIL, T., SHAPIRO, D. and FINK, M. Differentiation of psychotropic drugs by quantitative EEG analysis. Agressologie 9: 267-280 (1968)

ITIL, T. M., SHAPIRO, D.M., FINK, M. and KASSEBAUM, B.A. Digital computer classifications of EEG sleep stages. Electroencephalography and Clinical Neurophysiology 27: 76-83 (1969)

Various electronic analysis techniques have been used for quantitative analysis of the EEG during sleep, but due to the lack of reliability and the expense such procedures entail, they have not achieved general use (Knott et al. 1942; Kaiser et al. 1964; Hord et al. 1965; Maulsby et al. 1966; Agnew et al. 1967). The application of digital computer procedures the analysis of the sleep EEG, including power spectrum analysis, baseline cross analysis, phase detection, and averaging techniques, shows promise of greater reliability (Bickford 1959; Brazier 1961, 1965: Adey and Walter 1963; Burch et al. 1964; Fink and Shapiro 1965; Johnson et al. 1967; Walter et al. 1967).

We have successfully used on-line digital computer analyses for the identification and classification of EEG changes induced by psychotropic drugs (Fink et al. 1967, 1968; Itil 1968a; Itil et al. 1968a,b). Of the methods employed, analysis of the baseline cross of the primary EEG wave and its first derivative proved to be the most useful (Burch 1959; Burch and Fink 1964; Shapiro and Fink 1966); consequently, this technique has been used to objectively classify the EEG stages in all-night sleep recordings. This report summarizes our recent investigations and suggests pragmatic solutions to the problem of rapid and consistent analysis of EEG sleep stages.

ITIL, T., SHAPIRO. D., HICKMAN, C., FINK. M. and KIREMITCI, N. The differentiation of tranquilizers by quantitative EEG. Electrocncephalography and Clinical Neurophysiology 24: 288 (1968)

The majority of EEG studies in recent years have shown that tranquillizers induce various kinds of EEG changes. Investigations of more than 25 tranquillizers have demonstrated in the past that drug induced changes are related to the type of drug, dosage, method and speed of administration (Itil 1961, 1964). Compounds with different clinical effects produce EEG changes of different type and quantity.

In the present study using quantitative EEG analyses (power spectral density analysis with electronic frequency analyzer and period analysis with computer programs, IBM-1710), 3 tranquillizers with different chemical structures. pharmacologic. profiles and clinical effects were studied in normal volunteers and psychotic populations. Our investigations have shown that fixed body weight dosages of 3 tranquillizers (chlorpromazine, imipramine and chlordiazepoxide) given i.v. in a fixed amount of time produced signficant changes in the various EEG frequency patterns of a group of patients and volunteers in contrast to pre-drug records. Saline did not produce any significant EEG alterations in the same group. Statistical evaluation of the power spectral density analysis data demonstrated that chlorpromazine, imipramine and chlordiazepoxide induce significantly different EEG alterations than saline in the total group. Furthermore, each drug could be significantly discriminated from each other based on the various quantitative EEG changes. In addition to the power spectral analysis, period analysis results were obtained using the IBM-1710 and supplied additional information concerning the characteristic EEG effects and their time courses.

JACQUET, Y. Intracerebral administration of opiates. Methods of Narcotic Research. Edited by S. Ehrenpries and A. Neidle. New York: Marcel Dekker, Inc., 1974.

JACQUET, Y.F. and LAJTHA, A. CNS sites of morphine action: Hypo- or hyperalgesia depending on injection site and dose. Proceedings of the 3rd Annual Meeting of the Society for Neuroscience, Wards Island, New York, November 7-10, 1973.

Morphine is used therapeutically as an analgesic; yet very little is known about its CNS sites of action. Assays of different CNS regions following systemic administrations of morphine have failed to reveal any marked differential distribution of the drug. This may be due to the action of the "blood-brain" barrier, since it has been estimated that less than 0.1% of the administered dose reaches the CNS. By using fine-gauge cannula permanently implanted in various subcortical sites to inject morphine, we were able to deliver precise quantities of the drug to the intended sites. Morphine (10 mu-g) injected into the posterior hypothalamus (PH) and the 3rd ventricle resulted in significant hypo-algesia, while the same dose injected into the caudate, the medial septal nucleus, and the periaqueductal gray matter (PGM) in the mesencephalon yielded hyper-algesia. Of the latter three, the last resulted in the most marked hyper-algesia, with rats unable to tolerate a low level of foot shock which normal rats tolerate without even flinching. This same area has been reported to give rise to profound analgesia when electrically stimulated. Morphine has been shown to block the release of acetylcholine in peripheral and central tissues: thus its action here may be the opposite of electrical stimulation and may block cholinergic neural transmission in what has been suggested to be pain-inhibitory pathways.

Jacquet, Y.F. and Lajtha. A. continued

These results show that intracerebral injections of morphine differ in a significant manner from systemic injections of morphine, and result in either hypo- or hyper-algesia, depending on site and dose. These sites show specificity in that dextrorphan, the inactive isomer, had no effect at either the hypo-(PH) or hyper-(PGM) algesia sites.

JAFFE, J., DAHLBERG. C.C. and FELDSTEIN, S. Practical aspects of systematic research in psychoanalytic office settings: Report of to Committee on Research. Part IV: Research. Edited by J.H. Masserman. Science and Psychoanalysis, Vol. XI. New York: Grune and Stratton. 1967. Pp. 202-226.

JAMES, J. Female addictive research. Addictive Diseases: An International Journal (in press)

JATLOW, P.I. Analysis of drugs and toxicological agents. Gas Chromatography in Clinical Microbiology and Medicine. Edited by B. Mitruka and R. Kundargi. New York: John Wiley and Sons, 1975. Pp. 396-416.

The title "toxicological agents" has been interpreted in a narrow sense in preparing this chapter, which has been restricted to a discussion of drug analysis. Gas chromatography has been applied to the analyses of other categories of toxic compounds including carbon monoxide, pesticides, and organic mercury compounds. Gas chromatography with electron capture detection is. for example, the method of choice for identification and measurement of nanogram concentrations of chlorinated hydrocarbon pesticides.

Gas chromatography has or can be applied to almost every drug in use today. Although this chapter discusses relatively few of then. it touches on those drugs or drug categories that are in most common therapeutic use and which are most often of toxicologic interest. The analysis of these drugs is based on concepts which are readily applicable to the measurement of those agents that have been omitted.

JATLOW, P. Chlordiazepoxide analysis. Selected Standard Methods of Clinical Chemistry, Vol. 8. New York: Academic Press (in press)

JATLOW. P. A rapid ultraviolet spectrophotometric procedure for the analysis of drugs frequently involved in overdose emergencies. Manual of Analytic Toxicology, Vol. 2. Edited by I. Sunshine. Cleveland, Ohio: Chemical Rubber Company Press, Inc., 1971.

JATLOW, P. Toxicology. Gradwohl's Clinical Laboratory Methods and Diagnoses. Edited by A. Sonnenwirth and L. Jarett. St. Louis, Missouri: C. V. Mosby Company (in press)

JATLOW, P. Ultraviolet spectrophotometric analysis of barbiturates: Evaluation of potential interferences. American Journal of Clinical Pathology 59: 167-173 (1973)

Twenty drugs, including salicylic acid and sulfonamides, were studied to determine whether they interfered with the ultraviolet spectrophotometric analysis of barbiturates. These were drugs which have been cited as possibly or probahly interfering with this type of analysis. Only p-aminophenol, which would not be expected in blood in the free form, interfered. Ultraviolet spectrophotometry is suitable for the. emergency analysis of barbiturates in the hospital laboratory. It is recommended that the method selected utilize extraction at neutral pH, and differential spectrophotometry in which equal concentrations of drugs at pH 13 and pH 10 are compared directly with a single scan. The net difference between the absorbances measured at wavelengths of 260 nm. and 240 nm. is least subject to interference and can be used for quantification. At these wavelengths interference from other drugs is rare.

JATLOW, P. Ultraviolet spectrophotometric analysis of drugs in biological fluids. American Journal of Medical Technology 39(6): 231-236 (June, 1973)

The application of ultraviolet absorption spectrophotometry to the analysis of drugs in body fluids is reviewed. Its special suitability for hospital toxicology is emphasized. Rapid procedures which are suitable for the emergency analysis of barbiturates, chlordiazepoxide, glutethimide, and methaqualone in serum are described.

JATLOW, P. Ultraviolet spectrophotometric measurement of chlordiazepoxide in plasma. Clinical Chemistry 18: 516-518 (1972)

A simple ultraviolet spectrophotometric method is described for measurement of chlordiazepoxide in blood. The drug is extracted into chloroform at pH 7.4 and, after a NaOH wash, extracted back into HCI. The drug is identified by its characteristic ultraviolet spectra at acidic and basic pH's, and quantified from the absorbance value measured at the major acid peak of 247 nm. Although certain weekly basic drugs theoretically could interfere if present concurrently with chlordiazepoxide, we have not seen this during three years of experience. This procedure is easily combined with established methods for barbiturates and glutethimide. Specimens from more than 60 cases of documented chlordiazepoxide ingestion have had concentrations ranging from 0.2 to 6.6 mg/100 ml by this procedure.

JATLOW, P. I. and BAILEY, D. N. Gas chromatographic measurement of cocaine in plasma using a nitrogen detector. Clinical Chemistry (in press)

Cocaine, like most alkaloids, achieves relatively low plasma concentrations after its use. A nitrogen detector was employed because of its greater sensitivity and selectivity relative to flame ionization.

The internal standard (IS) was the propyl ester of benzoylecgonine, a homologue of cocaine. It was prepared in our laboratory by refluxing benzoylecgonine in n-propanol containing 0.3N HCl, with subsequent purification by preparative thin-layer chromatography. Four ml of plasma was extracted with heptane containing 2% isoamyl alcohol and IS. This was followed by back extraction into 0.1 N H_2SO_4, alkalinization with solid Na_2C0_3 - $NaHCO_3$ to pH 9.7, and re-extraction into solvent. The latter was evaporated at room temperature under air, and the residue, dissolved in methanol, was chromatographed at 255°C on a 3% OV-17 column. Cocaine standards in plasma were carried through the entire procedure. A model 3920 gas chromatograph (Perkin-Elmer Corp.) containing a nitrogen detector was used.

The precision (RSD) was 5.3% at an 0.05 ug/ml concentration. Although as little as 200 pg could be detected, negative sera showed a background equivalent to 0-.002 ug/ml cocaine.

The method was validated using plasma obtained from patients receiving mucosal applications of cocaine for local anesthesia. A level of 0.23 ug/ml was found 15 minutes after topical application of 100 mg.

JATLOW. P., McKAY. D. and SELIGSON, D. Computer assisted emergency analysis of drugs. Clinical Chemistry 18: 712 (1972)

A systematic approach to the emergency analysis of drugs in body fluids has been developed. The total procedure which is designed for emergency toxicology minimizes manipulations, provides qualitative and quantitative data, and uses a digital computer for interpretation, computation and reporting of data.

Data is entered by the technologist at a keyboard in response to computer instructions which relate to each analytic step. Location of major and minor absorption peaks (at two pH's in some cases), ratios of major to minor peak absorbances and peak absorbance values are used in the program for analysis of spectrophotometric data. Results are printed by the console printer or teletype at each stage of the analysis. A final lineprinter summary indicates drugs present (with concentration), drugs absent, and those not tested.

Following a single chloroform extraction at pH 7.4, drugs are partitioned into the following four groups for spectrophotometric analysis: barbiturates; other weak acids; bases; other benzodiazepines. Neutral drugs remaining in the solvent are analyzed by semiquantitative thin-layer chromatography. Alcohol and ethchlorvynol are determined in a single steam distillate by visible and ultraviolet spectrophotometry respectively. Drugs not easily detected in blood are identified in urine by calorimetric tests.

Choice of body fluids for analysis of each drug is consistent with its biological disposition. The chemistry and data processing are modular, and so can be abbreviated to meet the special needs of a specific case. The program has been applied on an in-laboratory computer, and modified for use on a terminal to a remote computer.

JATLOW, P. and SELIGSON, D. Application of a digital computer to emergency toxicology. Clinica Chimica Acta 50: 19-39 (1974)

A digital computer has been applied to the laboratory diagnosis of drug overdose. Analytic data is entered by the technologist at a keyboard in response to, computer instructions. Major and minor ultraviolet absorption peaks, pH dependent spectral shifts, and peak absorbance ratios are used for decision making. Data derived from thin-layer chromatography and calorimetric tests are used for drugs without sufficiently strong spectra. The program can be interrupted and re-entered at any point if additional analyses are required. Results are printed out at the terminal after each step. Upon completion of the screen a summary report lists drugs present (with concentration), absent, and not tested. This system has been developed primarily for application in the general hospital laboratory. The drugs or drug groups included in the program comprise well over 90% of those Involved in acute overdose.

JOE, G. W. Patient background indices for a drug-abusing population - development and distribution characteristics of a set of patient background index measures, based on the DARP population admitted to treatment between June 1969 and June 1971. Research on Patients, Treatments, and Outcomes. Edited by S. B. Sells. Studies on the Effectiveness of Treatments for Drug Abuse, Vol. 2. Cambridge, Massachusetts: Ballinger, 1974.

JOHNSON, J.C., GOLD, G.J. and CLOUET, D.H. An improved method for the assay of DOPA. Analytical Biochemistry 54: 129-136 (1973)

A modified dopa assay is described which increases sensitivity 100-fold over existing methods, so that as little as 1 ng of dopa/ml can be measured. The method involves KI-I_2 oxidation and catalysis of the fluorophore rearrangement by uv irradiation. The method is sufficiently sensitive to measure endogenous brain dopa levels.

KAIKO, R.F. and INTURRISI, C.E. Human biotransformation and excretion of orally administered cyclazocine: A method and its application. The Pharmacologist 15(2) (Fall, 1973)

Cyclazocine (C) is a narcotic antagonist currently under evaluation for the treatment of opiate dependence. A method employing solvent extraction and gas-liquid chromatography of trifluoroacetyl (TFA) derivatives has been developed for the quantitative determination of C and its biotransformation products. The separation of the TFA derivatives of C and norcyclazocine (NC) was achieved using 3% SE-30 as the stationary phase. As little as 40 ng can be recovered and quantitated by this method. Acid hydrolysis of the conjugated biotransformation products was carried out at 121° under pressure in an autoclave. Urine and plasma samples were collected from two patients receiving 1.9 mg of C every 12 hours. An average of 60% of the administered dose appeared in the total 12 hour urine as C and biotransformation products. This included an average of 21% of the dose as unchanged C, 24% as conjugated C, 4% as NC and 11% as conjugated NC. The applicability of this method to plasma samples was also demonstrated. These results indicate that both N-dealkylation and conjugation are routes of biotransformation for C in man.

KAIKO, R.F. and INTURRISI, C.E. The quantitation of cyclazocine and its metabolites in human urine by use of gas-liquid chromatography. Journal of Chromatography 100: 63-72 (1974)

A method is described for the quantitative determination of cyclazocine and its N-dealkylated biotransformation product, norcyclazocine, in human urine. The method can also be used to estimate the levels of conjugated cyclazocine and norcyclazocine by measurement of the amount of these compounds released by acid hydrolysis. The compounds are recovered from urine by the use of solvent extraction and separated as their trifluoroacetyl derivatives by the use of gas-liquid chromatography.

The levels of cyclazocine and metabolites were determined in the urine collected from two patients receiving 1.9 mg of cyclazocine every 12 h for the treatment of opiate dependence. Approximately 60% of the administered dose was recovered in patient urine as cydlazocine and metabolites. An average of 21% of the administered dose appeared in the urine as cyclazocine, 24% as conjugated cyclazocine, 4% as norcyclazocine and 11% as conjugated norcyclazocine.

KANANEN, G., OSIEWICZ, R. and SUNSHINE, I. Barbiturate analysis -- A current assessment. Journal of Chromatographic Science 10: 283-287 (May, 1972)

GC and UV/TLC procedures for barbiturate determinations yield clinically comparable analyses. Depending on the available personnel and equipment, one or the other may be used satisfactorily. When a large number of samples (20 or more) of barbiturate analyses are required, the described GC procedure is as reliable, but faster and more sensitive than the UV procedure. It involves extracting 1 ml of blood or urine with 5 ml of toluene containing aprobarbital as an internal standard. Any barbiturate in the toluene extract is then concentrated in 25 mu-l of 40% TMAH, an aliquot of which is injected into the gas chromatograph. The methylated barbiturates thus formed require 20 minutes for quantitative analysis.

KANDEL, D. Reaching the hard-to-reach: Illicit drug use among high school absentees. Addictive Diseases (in press)

While school surveys are based on students present on the days the surveys are conducted, resulting findings are interpreted as representative for youths enrolled in school in the particular ages sampled. As part of a large scale survey of adolescent drug use in the State of New York, two absentee studies were carried out to estimate levels of drug use among school absentees. Students interviewed in households reported very little drug use. By contrast, absentees self-selecting themselves to participate in a group administered questionnaire, reported much higher illicit drug use than regular students from the same schools. However, comparison of students in the absentee sample with the total target absentee population and the reverse association between drug use and selected background factors among absentees, suggests that most chronic absentees and heavy users, especially blacks and males, did not participate in the self-selected absentee sample. Attempts to identify factors related to higher drug use among absentees were unsuccessful. While poor school performance brings levels of illicit drug use among regular students to levels comparable to those of the absentees, poor school performance per se does not explain the higher rates of illicit drug use among absentees. It is clear that school absentees who are generally excluded from school surveys are extremely hard to reach for research pruposes.

KANDEL, D. Some comments on the relationship of selected criteria variables to adolescent drug use. Presented at the National Institute on Drug Abuse Drug Lifestyles Conference, St. Simons, Georgia, January, 1975.

KANTER. S.L., HOLLISTER, L.E., MOORE, F. and GREEN, D.E. Marihuana metabolites in urine of man. IV. Extraction procedures using diethyl ether. Research Communications in Chemical Pathology and Pharmacology 9(2): 205-213 (October, 1974)

A new extraction scheme has been described which separated urine samples into neutral, weak and strong acids fractions for studying marihuana metabolites by thin-layer chromatography. The weak acids fraction, previously ignored, has provided the cleanest separation of drug-related metabolites and in the greatest abundance.

KAUFMAN, J.J. Quantum chemical and theoretical techniques for the understanding of psychoactive drugs and narcotic agents. Proceedings of the International Conference on Computers in Chemical Research and Education. Ljublajana, Yugoslavia (in press)

KAUFMAN, J.J. and KERMAN, E. Quantum-chemical and theoretical techniques for the understanding of the action of drugs which affect the central nervous system. Jerusalem Symposia on Quantum Chemistry and Biochemistry 6: 524-547 (1974)

KAUFMAN, J.J. and KOSKI. W.S. Physicochemical, quantum chemical and other theoretical techniques for the understanding of the mechanism of action of CNS agents: Psychoactive drugs, narcotics and narcotic antagonists and anesthetics. Drug Design, Vol. V. Edited by E.J. Ariens. New York: Academic Press, 1971.

KENNEDY, J.S. and WADDELL, W.J. Whole-body autoradiography of the pregnant mouse after administration of ^{14}C-delta-9-THC. Toxicology and Applied Pharmacology 22: 252-258 (1972)

The distribution of ^{14}C-delta-9-tetrahydrocannabinol in pregnant A/JAX mice at 12 days of gestation was studied by whole-body autoradiography 0.33, 1, 3 or 24 hr after iv or 3 hr after sc administration, High concentrations of radioactivity were found after either iv or sc administration in liver, intestinal contents, Harder's gland, fat, corpora lutea, and adrenal cortex. The concentration was low in maternal brain and in the fetuses at all time intervals after injection. The fetal central nervous system had the highest concentration of all fetal tissues. The concentration was high in maternal lung and spleen after iv but not after sc administration.

KHAZAN, N. EEG correlates of morphine dependence and withdrawal in the rat. Drug Addiction: Experimental Pharmacology, Vol 1. Edited by J.M. Singh, L.H. Miller and H. Lal. Mount Kisco, New York: Futura Publishing Company, Inc., 1972. Pp. 159-172.

A morphine addiction cycle in rats prepared with chronically implanted cortical electrodes and i.v. cannulae has been described. Electroencephalographic (EEG), electromyographic (EMG) and behavioral monitoring revealed that, after the initiation of hourly automatic injections of morphine, sleep was greatly reduced and REM sleep virtually eliminated. During this period high voltage slow bursts of 4 to 7 Hz appeared in the EEG of the awake state. In the next stage, i.e., morphine dependence, when the rats self-injected the drug by pressing a lever, a state of behavioral wakefulness with EEG slow bursts prevailed immediately following an injection, while prolonged episodes of sleep and REM sleep predominated in the period preceding the next injection. During the ensuing stage of morphine withdrawal or abstinence, the amount of sleep decreased and became progressively superseded by a state of wakefulness and hyperirritability. The primary EEG manifestation accompanying the abstinence syndrome was a decline in the voltage output of the sleep-awake cycle, a phenomenon which correlated with the behavioral hyperirritability of the abstinent rats. Reduction in the voltage output of the sleep state was more pronounced and of longer duration than that of the awake or REM sleep states. After these initial changes peaked at the height of abstinence, a marked rebound in REM time developed, was accompanied by a rebound in the REM EEG voltage output, and remained evident throughout the 12 days of the study. Apart from the above, post-addict rats were found to display EEG and behavioral responses to morphine injection in a way markedly different from those of naive rats. Instead of the biphasic response of the naives, wherein initial stuporous behavior associated with high voltage EEG slow bursts was later followed by EEG and behavioral arousal, post-addict rats of 1 month exhibited a single phase of almost continuous and prolonged arousal. Although post-addict rats of 6 months tended to approach the biphasic pattern, these rats were still readily readily distinguishable from the naives simultaneously challenged. In contrast with the latter group receiving the first morphine challenge, post-addict rats which were given repeated challenges within periods up to one year following morphine withdrawal showed a more persistent arousal phase.

KHAZAN, N., COLASANTI, B. and KIRCHMAN, A. REM sleep during morphine dependence and abstinence in the rat: Pellet implantation versus i.v. administration. The Pharmacologist 13: 314 (1971)

Previous studies of morphine addiction in the rat utilizing the i.v. route (Khazan et al., J. Pharmacol. Exp. Ther. 155: 521, 1967) have demonstrated alterations both the amount and distribution of REM sleep. The present study was undertaken to determine the time course of such changes in rats implanted s.c. with morphine pellets and in i.v. rats. EEG and EMG recordings collected continuously revealed total suppression of REM sleep for up to 16-20 hours after pellet implantation. By the third day REM time had not only returned to normal but showed a tendency toward rebound as well. Upon withdrawal of the pellet 72 hours after implantation, the reduction in REM time within the first day, although not as pronounced, was comparable to that seen in rats addicted by the i.v. method. In contrast with i.v. rats, however, in which a rebound in REM sleep remained evident throughout the 12-day withdrawal period studied, REM rebound in post-pellet rats was maximal on the third day, with normal REM time reached by the fourth day. Thus, although the changes in REM sleep following both procedures are analogous, their time courses during dependence and abstinence suggest that the consequences in rats addicted to morphine by the i.v. method are more severe.

KIMIZUKA, H. and ABOOD, L.G. Interfacial adsorption of a psychotomimetic drug using liquid scintillation. Journal of Pharmaceutical Sciences 62(5): 740-745 (May. 1973)

A study was conducted on the oil-water partitioning and interfacial adsorption of ^{3}H-2-pyrrolidylmethyl N-methyl cyclopentylphenylglycolate (I), an anticholinergic psychotom metic agent. A new technique for radiotracer adsorption was developed involving the use of liquid scintillation counting. Among the physical parameters examined were partition coefficient, permeation constant, stability constant, and rate constant, of I in a two-phase system of water and a lipid, didodecyl phosphate (II). II greatly accelerated the rate of oil-water partitioning of I and exhibited interfacial absorption with I. The presence of polyanions, such as hyaluronic acid in the aqueous phase, promotes the transfer of drug from the oil to water phase. Equations found applicable to permeation of ions across membranes have been used to describe drug transfer through an oil-water interface.

KLEMM, W.R. A new, chronic experimental procedure for electrographic study of neuropharmacological mechanisms. Presented at Society for Neuroscience 4th Annual Meeting, St. Louis, Missouri, October 20-24, 1974.

A stable baseline of electrographic activity for studying drug mechanisms and actions is difficult, if not impossible, to achieve in the common methods that use animals which are either freely behaving, immobilized with muscle relaxant or surgically deafferented. A new experimental procedure for drug studies has been developed in which the EEG, multiple-unit activity, and averaged evoked responses seem to be unusually stable and free of artifacts. This procedure involves inducing a state of Immobility Reflex (IR) (also known as "animal hypnosis"). The IR is a reversible, involuntary, and an unconditioned reflex response in certain species to sudden change in afferent stimulation that results from the common method of simultaneous inversion and manual restraint. Because intact, chronically prepared animals are used, the same brain areas can be tested repeatedly with vehicle or different drug doses, administered either systemically or topically. The IR offers the unique combination of simplicity, of being non-surgical and non-traumatic, of reproducibility, and of relative freedom from behavioral variables.

KOKOSKI. R.J., SANDS, F.L. and KURLAND, A.A. Morphine detection by thin-layer chromatography in a urine-screening program. A comparison of ion-exchange-resin loaded paper extraction with direct solvent extraction. Committee on Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, 1969.

KOSERSKY, D.S. and HARRIS, L.S. Chronic intravenous drug administration in the pigeon. European Journal of Pharmacology (in press)

KOSTERLITZ, H.W., LESLIE, F.M. and WATERFIELD, A.A. Narcotic agonist and antagonist potencies of a homologous series of N-alkyl-norketobemidones measured by the guinea pig ileum and mouse vas deferens methods. Journal of Pharmacology 27: 73-78 (1975)

The narcotic agonist and antagonist potencies of the series of N-alkyl-norketobemidones from norketobemidone to decylnorketobemidone have been determined. The values obtained in the electrically stimulated preparations of the guinea-pig ileum and the mouse vas deferens are closely correlated. The agonist potencies observed in the guinea-pig ileum agree well with those found in the mouse hot-plate test (Oh-ishi & May) and those obtained by determining the inhibition of naloxone binding in brain homogenates (Wilson, Rogers, Pert & Snyder). The antagonist potencies in the guinea-pig ileum and, to a lesser extent, those in the mouse vas deferens agree with the values obtained in the morphine-dependent monkey.

KULLBERG, M.P. and GORODETZKY, C.W. Studies on the use of XAD-2 resin for detection of abused drugs in urine. Clinical Chemistry 20(2): 177-183 (1974)

We describe a procedure for extracting weakly acidic, neutral, and basic drugs from urine by using a column of XAD-2 resin. Adsorption of drugs from 20 ml of urine buffered at pH 8.5 ± 0.5 at a controlled flow rate of 2.5 ml/min was greater than 89% for all drugs tested except aspirin. On eluting the drugs tested with acetone and methanol/chloroform, recoveries ranged from 75 to 93%. Overall recoveries of drugs from urine to a thin-layer chromatography plate were between 63 and 78%. The concentration of morphine added to normal urine that can be detected 99% of the time (95% confidence limits) by this method was 80 (65-100) mu-g/liter. We evaluated three methods for recovering morphine from morphine glucuronide added to urine, by using appropriate modifications of the XAD-2 resin extraction method. Hydrolysis of urine, hydrolysis of urine extracts adsorbed on XAD-2 resin, and hydrolysis of urine extracts from the XAD-2 resin followed by a solvent extraction gave 75%, 40%, and 10% recoveries of morphine, respectively.

LATHES, V.G. On the use of reference substances in behavioral toxicology. Adverse Effects of Environmental Chemicals and Psychotropic Drugs: Quantitative Interpretation of Functional Tests. Edited by E. Frantik. Proceedings of the I.A.O.H. Study Groups on Functional Toxicity, Vol. I. New York: Elsevier, 1973. Pp. 83-88.

LAW, N.C. A modern approach for drug identification. American Journal of Medical Technology 39(6): 237-243 (June, 1973)

The experience that has been gained by using GC/MS system convinces us that for this type of analysis it cannot, at present, be challenged by any other method at least for identification in drug overdose cases.

The disadvantage, of course, is the cost of the instrument and its upkeep, making it impractical for a single hospital to undertake. However, as the number of acute overdoses increases, so do the number of types ingested, thus making treatment and analysis more difficult for the physician and analyst. There is no way to predict the physiological reaction to mixtures of newer and older drugs.

A C.I. mode is now under investigation and preliminary results are not yet conclusive.

LAW, N.C. and CEHRS, F.D. Four years of drug identification by gas chromatography mass spectrometry. Clinical Chemistry 20: 902 (1974)

LAWRENCE, R.H., JR. and WALLER. G.R. GC-MS/Probe-MS analysis of cannabinoids in resin glands of Cannabis sativa L. Proceedings of 13th Annual Meeting of the Phytochemical Society of North America, Pacific Grove, California, 1973. P. 24.

Glandular cells, stalked and sessile, are present on both vegetative and reproductive parts of Cannabis sativa L. plants. These glandular cells secrete a resin which we have found to consist mainly of cannabinoids, with minor amounts of monoterpenes and sesquiterpenes. Our interest in cannabinoid biosynthesis in Cannabis has stimulated us to study the cannabinoid content of these glandular cells. Resin gland cells from stems, leaves, female flower bracts and male flower sepals and anthers of C. sativa L. plants were collected by microdissection. The gland cells were placed in hollow glass beads for solid injection for GC-MS analysis (3% OV-17 Chrom W(HP), 5. 5' x ¼"; LKB-9000) or in glass sample holders for direct probe-MS analysis. Two C. sativa L. variants, Mexican (M-A2, drug phenotype) and Turkish (T-A2, non-drug phenotype), were studied. Major differences in cannabinoid content of anther glands in comparison to leaf, stem, and bract glands were observed in relation to delta^{1}-THC/CBD ratio in the Turkish variant, and to a major heterogeneous GC peak with molecular ions of m/e 310, 314, 316) in the Mexican variant. A detailed analysis of major and minor cannabinoids in resin glands will be presented.

LAWRENCE, R.H., JR. and WALLER, G.R. Glandular structures of Cannabis sativa L. and cannabinoid production. Presented at the 50th Annual Meeting of the American Society of Plant Physiologists, Cornell University, Ithica, New York. Plant Physiology 53: 5-13 (1974)

Two types of glandular structures develop on the epidermis of Cannabis sativa L., elongated unicellular hairs (UH) and multicellular capitate glands (MG). Both types occur on the epidermis of stems, leaves, braces of female flowers and sepals of male flowers. Hypocotyl epidermis develops only UH and cotyledons show no glandular development. Direct analysis by GC-MS of cap cells dissected from MG reveals that these cells accumulate cannabinoids (as carboxylic acids), monoterpenes, and sesquiterpenes in high concentration. Cannabinoids appear to be associated with only the MG and are not present in UH nor in tissues devoid of MG (hypocotyls, cotyledons, roots, pith, and xylem). Our results lead to the tentative hypothesis that cahnabinoid biosynthesis occurs in the stalk or basal cells of the MG resulting in accumulation in the cap cells. A possible exception to the above appears to be in tissue cultures of Cannabis recently established in our lab. These cultures contain cannabinoids but do not develop glands.

LAWRENCE, R.H., JR. and WALLER, G.R. The role of specialized epidermal glands in the production of cannabinoids in Cannabis sativa L. Proceedings of the 9th IUPAC International Symposium on Chemistry of Natural Products, Ottawa, Canada, Abstract 24c, 1974.

The occurrence of natural products in specialized epidermal cells of plants is a common phenomenon. In Cannabis sativa L. two types of epidermal glandular structures develop, elongated unicellular hairs and multicellular capitate glands. Data is presented which indicates that cannabinoids are associated with the multicellular capitate glands and that tissues devoid of these glands appear to lack cannabinoids. Additional data is presented which suggest that cannabinoid biosynthesis may occur in the stalk and/or basal cells of the multicellular glands resulting in accumulation in the cap cells. Gas chromatography-mass spectrometry (GC-MS) analysis of compounds (associated with specific cell types) utilizes a recently developed all glass, solid injection system which permits direct analysis of cells without solvent extraction. Cells for analysis are collected from the plant by microdissection and placed in hollow glass beads for injection into the GC-MS. To detect cannabinoids present as carboxylic acids their trimethylsilyl derivatives are formed by exposing injector beads containing glandular cells to N,O-bis-(trimethylsilyl)-acetamide vapor at 40°C for 5 minutes prior to injection. Recent experiments with Cannabis cell cultures are also discussed.

LAWRENCE, R.H., JR., WALLER, G.R. and KINNEBERG, K.F. An improved method of sample introduction in gas chromatography-mass spectrometry of biological materials. Analytical Biochemistry 62(1): 102-107 (November, 1974)

In the GC-MS analysis of biological materials the method of sample introduction is an important factor affecting the value of the information obtained. A method has been developed which utilizes small glass beads as sample holders which are introduced into the GC column by way of a gas-tight, Teflon stopcock. This glass sample holder introduction system is very simple to construct and, in GC-MS analysis, offers advantages over other methods of sample introduction.

LEAFE, T.D., SARNER, S.F., WOODLAND, J.H.R., YOLLES, S., BLAKE, D.A. and MEYER, F.J. Injection method for delivery of long-acting narcotic antagonists. Narcotic Antagonists. Edited by M.C. Braude, L.S. Harris, E.L. May, J.P. Smith and J.E. Villarreal. Advances in Biochemical Psychopharmacology, Vol. 8. New York: Raven Press, 1973.

Cyclazocine-poly(lactic acid) composites in small particle form were implanted as well as injected into rats and the amounts of cyclazocine released were determined at various intervals of time. The results obtained by the injection method are comparable to those given by implantation. The former method is preferable because it makes surgical incision unnecessary. Particle size, within the dimensions investigated, appears to show small differences on the release rate of cyclazocine.

LEANDER, J.D. and McMILLAN, D.E. Substantial oral morphine intake by the rat using schedule-induced polydipsia. Federation Proceedings 32: 726 (1973)

Rats were trained to lever press under a fixed-interval 90-sec schedule of food pellet presentation. A water bottle was freely available, and all animals developed the typical pattern of excessive post-pellet drinking (consuming approximately 30 ml/hr). Initial exposure to various morphine solutions decreased drinking but increased lever pressing. The average dose of morphine consumed using concentrations of 0.3, 0.56, and 1.0 mg/ml was 10 mg/kg during a one hr session. After 2 weeks of exposure during daily 4 hr sessions to morphine solutions of 0.25 and 0. 5 mg/ml, there was little change (as compared to the water solution) in average lever-pressing rate; a slight dose-dependent decrease in drinking rate; and an appreciable dose-depepdent increase in total dose consumed. During the last 3 days of exposure to 0.25 mg/ml, the average dose consumed was approximately 75 mg/kg/4 hr session. After working up to a solution of 1.0 mg/ml, the average dose consumed was 200 mg/kg/4 hr session. The stable pattern of drinking exhibited by rats chronically maintained on a 0.5 mg/ml solution was a tendency for drinking to no longer reliably be a post-pellet phenomenon, but to be long drinks spaced throughout the 4 hr session. Thus, schedule-induced polydipsia can be used to induce rats to chronically consume large doses of morphine orally.

LENTZ, P.L., TURNER, C.E., ROBERTSON, L.W. and GENTNER, W.A. First North American record for Cercospora Cannabina, with notes on the identification of C. Cannabina and C. Cannabis. Plant Disease Reporter 58(2): 165-168 (February, 1974)

Late in August 1972, a fungal disease appeared in an experimental planting of Cannabis sativa in Oxford, Mississippi. The causal organism was Cercospora cannabina, which was previously unrecorded from North America. The only other known Cercospora on Cannabis is C. cannabis, recorded in the United States in Wisconsin and Missouri. Comparison of the Mississippi fungus with the American collections of C. cannabis showed significant dissimilarities in growth habit and in characteristics of conidiophores and conidia.

LIN, C.H., BRAVERMAN, S., KEINATH, S., TRESK, R. and ADLER, M.W. Anticonvulsant action of acute morphine administration in rats. Federation Proceedings (in press)

LINDER. C. and FISHMAN, J. Narcotic antagonists. 1. Isomeric sulfate and acetate esters of naloxone (N-allylnoroxymorphone). Journal of Medicinal Chemistry 16(5): 553-556 (1973)

The synthesis of the two isomeric monosulfates lb, c and the disulfate ld esters of naloxone is described. These and the corresponding acetates le-g were prepared as potentially longer acting narcotic antagonists than naloxone itself. The sulfation and acylation reactions appeared to reflect group interactions within the naloxone molecule. Intravenous administration to rats showed the acetates to have the same range of antagonistic potency as naloxone, with respect to the reversal of morphine-induced respiratory depression. By oral administration the acetates appeared to be several-fold more potent as well as longer acting than naloxone in preventing respiratory depression induced by morphine. In both intravenous and oral administration to rats, the sulfate esters proved inferior to naloxone in both potency and duration of action. Neither the acetates nor sulfates had any agonistic properties at relatively high iv dosages.

LIU, C-T. and ADLER, F.L. Immunological studies on drug addiction. I. Antibodies reactive with methadone and their use for detection of the drug. Journal of Immunology 111: 472 (1973)

LLOYD, S.C., ASNIS. S.F., HAMMOND, W.E. and ELLINWOOD, E.J., JR. Drug abuse record keeping system with an interactive computer, II: The GEMISCH method. Committee on the Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council, 1972.

LOEFFLER, K.O., GREEN, D.E., CHAO, F-C. and FORREST, I.S. New approaches to assay of cannabinoids in biological extracts. Proceedings of the Western Pharmacological Society (in press)

LOEW. G.H., BERKOWITZ, D., WEINSTEIN, H. and SREBRENICK. S. Quantum chemical studies of morphine-like opiate narcotics: Effect of polar group variations. Molecular and Quantum Pharmacology. Edited by E. Bergmann and B. Pullman. Dordrecht, the Netherlands: D. Reidel Publishing Company, 1974.

LOH, H.H., CHO, T.M. and LIPSCOMB, W. Estimation of morphine by polyamide mini thin-layer chromatography. Journal of Chromatography 76: 505-508 (1973)

LOWY, K., WEISS, B. and ABOOD, L.G. Influence of an anticholinergic psychotomimetic agent on behaviour in cats controlled by an auditory stimulus. Neuropharmacology 13: 707-718 (1974)

An anticholinergic psychotomimetic agent was examined for its behavioural effects on cats trained to press a lever, the location of which corresponded to one of two sound sources. The cats were trained to lick a protruding sponge in dim light which then caused the main light to turn on, and an auditory signal to be emitted from either side of a panel in the chamber. Any lever response terminated the trial. A food reward was given only if the cat pressed a lever on the same side as the sound signal. A new trial cycle began when the cat licked the sponge. A computer programme controlled the experiment, stored we experimental data, and permitted an analysis of various psychophysical parameters, such as ability to localize an auditory cue, threshold of sound intensity, rate of trial onset, and lateral tendency. Doses of 10-20 mu-g/kg, N-methyl 4-piperidylcyclobutylphenyl glycolate (CBG) reduced the number of responses, and tended to lower the relative time spent in the light period. However, at lower doses CBG produced a marked increase in some cats in total number of trials. Higher doses of scopolamine also reduced total trials, but less consistently. An increase of the number of responses was not observed. A number of animals exhibited a lateral preference for either the right or left lever. CBG, but not scopolamine, markedly shifted this lateral tendency in some cats. The results are discussed in relation to the central effects of the glycolate esters in man.

LYNN, R.K., SMITH, R., OLSEN, G.D., LEGER, R.M. and GERBER, N. Studies of the metabolism of methadone (M) and methodology for isolation and quantification of the drug and its primary metabolite, 2-ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidine (P) using gas chromatography (GC) and mass spectrometry (MS). Federation Proceedings (in press)

A specific GC assay has been developed for the quantification of M and P. The method involves extraction of M and P with 1-chlorobutane from tissue (human plasma, mouse homogenate, perfusate) at pH 9.8, re-extraction of an aliquot of solvent with 0.1 N HCl, alkalinization and final extraction into chloroform. The partition coefficient of M determined by 4 tube counter current distribution between 1-chlorobutane and pH 9.8 buffer (volume ratio 1:3) is greater than 70. Mice pretreated with phenobarbital showed a twofold increase in the rate of metabolism of M at 15 min. In the perfusate of the isolated perfused rat liver there was an initial rapid decline of M followed by a slower decline (t/2 114 min) after 30 min. Small quantities of M and P were eliminated in the bile. Concentration of P in the mouse and the perfusate increases with time. GC-MS of the methylated (CH_3I, $DMSO^-$) glucuronic acid conjugates from bile gave molecular ions at m/e 525 and 555 indicating the presence of mono- and di-hydroxylated P glucuronides. GC-MS demonstrated the presence of other hydroxylated metabolites. M was quantitated in the plasma of M tolerant subjects.

MCAULIFFE, W.E. and GORDON, R.A. A test of Lindesmith's theory of addiction: The frequency of euphoria among long-term addicts. American Journal of Sociology 79(4): 795-840 (January, 1974)

Lindesmith and others claim that once physical dependence is established addicts do not experience euphoria. Consequently, euphoria cannot explain chronic addiction. Data are presented to show that, contrary to this view, long-term addicts experience euphoria frequently, crave it, and act to obtain it. "Lack of money" is the most important reason addicts give for not experiencing euphoria more often. Based on success in achieving euphoria, two classes of addicts are identified. The sources of income of addicts who experience euphoria most often correspond to those of types described by others as highest in prestige. Analysis suggests an addict stratification system founded on the two major psychopharmacological phenomena of opiates: withdrawal and euphoria. Addicts who barely succeed at tending to their daily need to avoid withdrawal are lowest in prestige. In the higher prestige ranges, addicts are stratified by their success in achieving euphoria. Thus, the social as well as the value system of addicts owes much to success at achieving what are universally considered, at the individual level, to be the most fundamental reinforcers. Since these reinforcers operate at the individual level, our analysis reveals the addict social system as a microcosm of broader theoretical interest, with transitions between physiological, psychological, cultural, economic, and sociological phenomena in plain view.

McCLUNG, R., DAFNY, N. and BURKS, T.F. Effects of morphine and naloxone on CNS field in unanesthetized rats. Federation Proceedings (in press)

Evoked field potentials in response to acoustic stimulation were recorded from freely behaving animals before and after intraperitoneal injections of morphine (10 mg/kg, 30 mg/kg or 50 mg/kg). Sites of recording were: cochlear nucleus, septum, substantia nigra, raphe nucleus, pineal body, caudate nucleus and ventromedial hypothalamus. The most consistent effects of morphine occurred in the pineal body and caudate nucleus. The amplitude of the field potentials in response to acoustic stimulation were consistently increased in the pineal body at all dose levels of morphine. This effect of morphine was reversed upon administration of naloxone (1 mg/kg). Responses in the caudate nucleus to acoustic stimulation were related to the dose of morphine administered. Smaller doses of morphine (10 and 30 mg/kg) decreased the amplitude of field potentials, while 50 mg/kg of morphine resulted in an increase in the amplitude of the response, Subsequent naloxone administration resulted in response amplitudes similar to controls. Effects of morphine on field potential responses to acoustic stimulation in the other recording sites were more variable. Effects of morphine on responses of the pineal body and caudate nucleus to acoustic stimuli were attenuated by prior administration of naloxone. These results indicate that morphine can act selectively to produce changes in evoked field potentials in specific brain structures.

McISAAC, W.M., HARRIS, R.T. and HO, B.T. The indole hallucinogens. Advances in Mental Science, Drug Dependence, Vol. 2. Austin, Texas: University of Texas Press, 1969. Pp. 41-54.

McMILLAN, D.E. Physical dependence in rats after drinking narcotic analgesics. Federation Proceedings (in press)

Narcotics were placed in the drinking water of rats during a 12-day period. The average daily intake was 34 and 100 mg/kg of morphine (0.3 and 1.0 mg/ml), 11 and 41 mg/kg of levorphanol (0.1 and 0.3 mg/ml), 28 and 72 mg/kg of meperidine (0.3 and 1.0 mg/ml), 38 and 62 mg/kg of methadone (0.3 and 1.0 mg/ml), and 0.5 and 1.4 mg/kg of etonitazene (3 and 10 mu-g/ml). When 1 mg/kg of naloxone was administered after 12 days of drug drinking, the rats drinking morphine, etonitazene and 1.0 mg/ml of meperidine lost almost 40 gms in weight during the first 6 hours, while rats drinking levorphanol lost about 20 gms and rats drinking methadone, or 0. 3 mg/ml of meperidine lost about 10 gms. Rats drinking morphine, etonitazene or levorphanol increased drug intake during the 24 hours after naloxone, while rats drinking meperidine or methadone did not. After 15-17 days of drug drinking the rats were switched to water. The body weights of the ex-drinkers of morphine, etonitazene, or levorphanol decreased about 40 gms in two days, with gradual recovery in about a week, but ex-drinkers of methadone or meperidine only gained weight. During the 24 hours after the switch to water, the fluid intake of ex-drinkers of morphine or etonitazene decreased, that of ex-methadone drinkers increased and that of ex-drinkers of levorphanol or meperidine did not change.

McMILLAN. D.E., WADDELL, F.B. and CATHCART, C.F. Establishment of physical dependence in mice by oral ingestion of morphine. The Journal of Pharmacology and Experimental Therapeutics 190(2): 416-419 (1974)

Morphine solutions were the only drinking solutions available to mice for 13 days. During the last 9 days of drinking a 1.0 mg/ml of morphine solution, the mice averaged a daily morphine intake of approximately 150 mg/kg. When injected with naloxone, the mice showed characteristic abstinence jumping, diarrhea, weight loss and abnormal posturing, suggesting that physical dependence had been produced by the morphine ingestion.

McRAE, D.J. Development of a patient topology. Research on Patients, Treatments, and Outcomes. Edited by S. B. Sells. Studies of the Effectiveness of Treatments for Drug Abuse, Vol. 2. Cambridge, Massachusetts: Ballinger, 1974.

MAICKEL, R.P., BRAUNSTEIN, M.C., McGLYNN, M., SNODGRASS, W.R. and WEBB, R.W. Behavioral, biochemical, and pharmacological effects of chronic dosage of phenothiazine tranquilizers in rats. The Phenothiazines and Structurally Related Drugs. Edited by I.S. Forrest, C.J. Carr and E. Usdin. New York: Raven Press, 1974.

The data presented herein indicate that a variety of biochemical, behavioral and pharmacological effects are seen when rats are chronically dosed with phenothiazine tranquilizers. The drugs accumulate in plasma and tissues. Concomitant with this accumulation are moderate elevations in liver glycogen and triglycerides, extrapyramidal symptoms, and various types of behavioral adaptations. Since many of these effects cannot be correlated with brain levels of drugs themselves, further study of the possible role of active metabolites appears to be a necessity.

MAICKEL. R.P., FEDYNSKYJ, N.M., POTTER, W.Z. and MANIAN, A.A. Tissue localization of 7- and 8-hydroxychlorpromazines. Toxicology and Applied Pharmacology 28: 8-17 (1974)

The time course of physiological disposition of ^{3}H-labeled 7-hydroxychlorpromazine and 8-hydroxychlorpromazine has been examined in rats after a single dosage, and the accumulation of each compound has been studied after 6, 14 and 28 doses on a bid schedule. The 8-hydroxycompound decays at a slower rate and shows a greater degree of accumulation on repeated dosage than does the 7-hydroxychlorpromazine. Both compounds enter the brain (the 7-hydroxy to a greater extent) and distribute uniformly, with no significant overt behavioral effects. Both compounds caused significant liver and kidney damage as demonstrated by histological evaluation.

MAICKEL, R.P., LEVINE, R.M. and QUIRCE, C.M. Differential effects of d- and l-amphetamine on spontaneous motor activity in mice. Research Communications in Chemical Pathology and Pharmacology 8(4): 711-714 (August, 1974)

The effects of single doses of d- and l-amphetamine on motor activity in mice differed both in quantitative and qualitative aspects. At low doses (0. 5 mg/kg, i.p.) and at high does (8.0 mg/kg, i.p.), both isomers were stimulants of SMA, differing only in potency. However, at intermediate doses (2.0, 4.0 mg/kg. i.p.) the l-isomer caused a significant depression of SMA while the d-isomer was stimulatory.

MAICKEL, R.P., ROMPALO, A.M. and COX. R.H., JR. Differential effects of monoamine oxidase inhibitors. Research Communications in Chemical Pathology and Pharmacology 8(4): 727-730 (August, 1974)

Chronic dosage of rats for 20 days with non-toxic doses of different monoamine oxidase inhibitors had clearly differential effects on brain biogenic amines and spontaneous motor activity. No correlation could be seen between behavioral and biochemical effects of the drugs.

In summary, the current social recognition and acknowledgement of euphoria as a desired and sought after affect state in man has been discussed. A group of drugs has been described which appear to produce this sort of state in man and which bear an interesting resemblance to two major naturally occurring neurotransmitter families. In addition, we have reported the possibility that at least one of these compounds can be synthesized in brain via a newly described N-methylation pathway. It appears there is a major obstacle to the use of euphorogens as a chronic management technique which relates to the multifaceted nature of the brain's metabolic adaptational processes. These adaptational processes are currently being looked at in two ways: (1) The possibility of purposely inducing these adaptational processes with the behavioral and subjective concomitants of these adaptations being the end product of the chemical maneuver; (2) The possibility of chemically and hormonally altering or inhibiting the rate of adaptation the brain makes to these new treatments.

It appears that the age of euphorogens is upon us and we are coming to it with a far greater understanding of brain biology than in eras involving other drug families and other affect states. It will be exciting times indeed for those in the brain sciences. It wouldn't be a surprise if over the next few years a wide variety of drugs that produce euphoria will be available for use. The question about who will be in charge of them when they will be used and how they will be used I think probably reaches beyond the area that is legitimately the purview of a brain scientist or psychiatrist. Whether they can ever be used effectively except on a periodic basis will await further research. It's perhaps philosophically important that drug-induced pleasure habituates so quickly. It calls to mind a recent statement Heinz Lehman made after hearing about some of this work: "It seems to me that puritanical attitudes toward pleasure must have as part of their bases these neurobiological mechanisms of adaptation."

MANNO, B.R. and MANNO, J.E. 11-hydroxy-delta-9-tetrahydrocannabinol induced changes in the perfused rat heart. Presented at the Meeting of the Society of Toxicology, Williamsburg, Virginia, Spring, 1975.

The effects of 11-hydroxy-delta-9-tetrahydrocannabinol (11-OH-delta-9-THC) on the myocardium and the coronary vasculature have been evaluated using the isolated perfused rat heart. The 11-OH-delta-9-THC was suspended in a vehicle of 1.5% Tween 80, 5% ethanol and water and doses ranging from 0.1 to 28 micrograms were infused over a 3 minute period. Hearts were monitored for changes in rate, force of contraction and perfusion pressure continuously during the infusion period and for 20 minutes after the infusion of 11-OH-delta-9-THC ceased. Heart rate fluctuations ranging from 3 to 5% of control occurred but were not considered to be significant. With low concentrations of 11-OH-delta-9-THC, an initial slight increase in the inotropic response (less than 5% of control) occurred followed by a negative inotropic response (less than -6% of control). Only a negative inotropic response occurred at high concentrations of 11-OH-delta-9-THC (up to 20% of control). Perfusion pressure, an index of coronary vasculature resistance, increased slightly with most doses of the drug (up to 10% of control). With doses of 25.5 and 28 micrograms of 11-OH-delta-9-THC, a biphasic response occurred. Initially, a decrease (vasodilation) was observed (-15 and -9% of control) followed by an increase in perfusion pressure (vasoconstriction) not exceeding 10% of control. The data indicate that 11-OH-delta-9-THC has little direct effect on heart rate, however, it does produce a negative inotropic response on the myocardium with a subsequent decreased coronary vasculature resistance followed by increased vasculature resistance.

MANNO, B.R. and MANNO, J.E. The marihuana dilemma: Has it been resolved? Toxicology Annual. Edited by C.L. Winek. New York: Marcel Dekker, Inc. (in press)

MANNO, B.R. and MANNO. J.E. Some cardiovascular actions of delta-9-tetrahydrocannabinol in the rat. Toxicology and Applied Pharmacology 25: 451 (1973)

The mechanism of the highly reproducible, delta-9-tetrahydrocannabinol (delta-9-THC) dose-related tachycardia in humans who have smoked marihuana remains obscure. This work was initiated as one phase of a study to differentiate the centrally mediated versus direct myocardial and vascular effect of delta-9-THC. Hearts from decapitated rats were perfused by a modified Langendorf technique with a modified Krebs-Henseleit bicarbonate medium, pH 7.4. A10-g diastolic tension was maintained on the spontaneously beating heart for the duration of the experiment. Force of contraction and coronary perfusion pressure changes were also monitored. Twelve doses of delta-9-THC(1.04 x 10^{-5}M) were infused into the hearts for 3-min intervals. No chronotropic change was observed at any dose of delta-9-THC used. Alterations in both inotropic response and coronary vasculature resistance were observed. As the concentration of delta-9-THC increased, a negative inotropic effect of as much as -26% of control was observed. The vasculature resistance denoted by changes in perfusion pressure produced a biphasic response. Concentration of delta-9-THC from 1.04 x 10^{-9} to 2. 91 x 10^{-6}M were vasoconstrictive with increases in pressure as much as +33% of control. Delta-9-THC concentrations of 2.65 x 10^{-6} to 1.04 x 10^{-5}M produced a decrease in pressure of as much as 34% of control indicating vasodilation. These studies using varied concentrations of delta-9-THC in isolated perfused hearts indicate that (1) the delta-9-THC dose-related tachycardia is not a direct effect on the myocardium; (2) a direct myocardial inotropic effect was induced by low concentrations of delta-9-THC and (3) a direct coronary vasculature effect was produced by delta-9-THC and (4) a direct coronary vasculature effect was produced by delta-9-THC.

MANNO, J.E. and FORNEY, R.B. Drug effects on motor performance. Principles and Techniques of Human Experimentation. Edited by E.G. McMahon. Mount Kisco, New York: Futura Publishing Company (in press)

MANNO, J.E., KIPLINGER, G.F., RODDA, B.E., FORNEY, R.B. and MANNO, B.R. Dose-dependent alterations in human motor and mental performance after smoking marijuana cigarettes. Chapter 1 of Drug Addiction: Clinical and Socio-legal Aspects, Vol. II. Edited by J. Singh. Mount Kisco, New York: Futura Publishing Company, 1972. Pp. 3-11.

MANNO, J.E. and MANNO, B.R. The interaction of delta-9-tetrahydrocannabinol (THC), pentobarbital and SKF-525A with the cardiovascular system of the rat. Federation Proceedings 32: 755 (1973)

Aqueous suspensions of THC were administered intravenously to male rats in doses of 0.05 mg/kg and 0.5 mg/kg. Direct arterial blood pressure and heart rate were continuously monitored from indwelling carotid catheters in pentobarbital anesthetized and unanesthetized. non-restrained animals. Control rats were administered saline and monitored in the same manner as the experimental animals. A similar series of experiments investigated the effect of pretreatment with the metabolic inhibitor SKF-525A (beta-diethylaminoethyl diphenyl propylacetate). A maximal bradycardia was produced in all conditions at 10 minutes after THC administration. The bradycardia reverted to a tachycardia at 60 minutes in unanesthetized rats. The initial bradycardia was greater in anesthetized animals than in unanesthetized rats. Pretreatment with SKF-525A potentiated the initial negative chronotropic action of THC, particularly in unanesthetized rats. The tachycardia at 60 minutes was also potentiated by SKF-525A. The implications of the pretreatment of SKF-525A will be discussed with reference to alerations in THC and 11-hydroxy THC concentrations as described by Gill and Jones (Biochem. Pharm. 21: 2237, 1972).

MANNO. J., MANNO, B., WALSWORTH, D. and HERD. R. Analysis and interpretation of the cannabinolic content of confiscated marihuana samples. Journal of Forensic Sciences 19(4): 884-890 (1974)

Confiscated marihuana samples from a three-year period were assayed quantitatively for their concentrations of delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN) by gas chromatography. A wide variability in the concentrations of the cannabinols was observed and a steady increase in potency of the samples was evident in the more recently confiscated specimens. The concentration of THC, CBN, and CBD and their ratios can be used to relate the approximate age of the sample (time from harvest), the potential source of the marihuana, and its potency. The relationships and their significance are discussed.

MELIKLAN. A.P., GREEN, D.E., SKINNER, J.L. and FORREST, I.S. Isolation of in vivo delta-9-tetrahydrocannabinol metabolites from primate urine. Proceedings of the Western Pharmacological Society 16: 234-239 (1973)

MELLET, L.B. and STROBEL, J. An electrophoretic study of acute and chronic drug effects. Bulletin, Problems of Drug Dependence 30: 5376-5391 (1968)

MERLIS, S. Problems and experiences with drug trials outside the United States. Diseases of the Nervous System 35(7): 5-7 (1974)

MILLER, L.L., editor. Marijuana. Effects on Human Behavior. New York: Academic Press, 1974.

This book summarizes recent scientific evidence concerning the effects of marijuana on human behavior. It not only reviews acute and chronic laboratory effects of cannabinoids on cognition and psychomotor performance, but covers more controversial topics: the relationship of marijuana use to aggressive behavior, progression to more dangerous drugs of abuse, the development of psychiatric illness, and effects on driving.

The book places emphasis on the unbiased summary and interpretation of relevant data on a given topic. Many of its fourteen chapters cover new and original material not previously published. It will be of interest to clinical investigators and researchers in pharmacology, as well as psychologists, psychiatrists, sociologists, lawyers and legislators.

MISRA, A.L., VADLAMANI, N.L. and MULE, S.J. Chromatographic separation of methadone, some of its metabolites and congeners. Journal of Chromatography 67: 379-381 (1972)

MOLE, M.L., BUELKE, J. and TURNER, C.E. Preliminary observations on cardiac activities of Cannabis sativa L. root extracts. Journal of Pharmaceutical Sciences 63(7): 1169-1170 (July, 1974)

MOLE, M.L., JR. and TURNER, C.E. Phytochemical screening of Cannabis sativa L. II. Choline and neurine in the roots of a Mexican variant. Acta Pharmaceutica Jugoslavica 23(4): 203-205 (1973)

The presence of nitrogen containing components in Cannabis sativa L. has been reported by various workers. Jahns isolated choline, Schulze and Frankfurt and Merz and Bergner isolated choline and trigonelline, Kwasniewski suggested the presence of muscarine and Obata, et.al. identified piperidine. Lousberg and Salemink have reported the isolation of a compound containing a betain type moiety; however, full structural details have yet to be reported. Also, Rapoport, et.al. isolated small amounts of four alkaloids which were subjected to high resolution mass spectrometry; but no conclusions about the total structures could be drawn from the limited data. In recent communications from these laboratories, Slatkin confirmed the presence of N-(p-hydroxy-beta-phenylethyl)-p-hydroxy-trans-cinnamamide and Turner and Mole reported the isolation of L.-proline. We wish now to report the isolation and characterization of the quaternary alkaloid neurine. The presence of choline has also been confirmed.

MOLE, M.L., JR. and TURNER, C.E. Phytochemical screening of Cannabis sativa L. I: Constituents of an Indian variant. Journal of Pharmaceutical Sciences 63(1): 154 -156 (January, 1974)

Delta-9-trans-tetrahydrocannabivarin, a mixture of sterols (campesterol, stigmasterol, and beta-sitosterol), and the amino acid. L-proline were isolated from an Indian variant of Cannabis sativa L. Characterizations were accomplished by the usual spectral methods, except for the sterols which were subjected to GLC-mass spectral analysis.

MOON, J.H., STARK, J.D., SUN, C.D. and WOODS, J.H. Computer controlled drug self-administration facility. Committee on the Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council, 1973. P. 788.

This paper describes the development of a computer controlled drug self-administration facility for rhesus monkeys.

MORETON, J.E. and DAVIS, W. M. A simple method for the preparation of injectables of tetrahydrocannabinols and cannabis extracts. Journal of Pharmacy and Pharmacology 24: 176 (1972)

MULE, S.J. and MISRA, A.L. Disposition and metabolism of levo-metadone-1-methyl-^{3}H in the rat. Federation Proceedings 31: 528 (1972)

MULE, S.J., SUNSHINE, I., BRAUDE, M. and WILLETTE, R.E., editors. Immunoassays for Drugs Subject to Abuse. Cleveland, Ohio: Chemical Rubber Company Press, Inc., 1974.

This monograph consists of the proceedings of a meeting on Immunoassays for Drugs Subject to Abuse held under the sponsorship of the Center for Studies of Narcotic and Drug Abuse, National Institute on Drug Abuse, Rockville, Maryland. The meeting brought together a select group of outstanding people actively engaged in the development or the evaluation of immunoassay techniques for the detection of drugs of abuse. The presentations are limited to general methodologies and essentially omit technical details as applied specifically to each drug of abuse, as these have already been published.

NYBACK, H., SCHUBERT, J. and SEDVALL, G. Effect of apomorphine and pimozide on synthesis and turnover of labelled catecholamines in mouse brain. Journal of Pharmacy and Pharmacology 22: 622-624 (1970)

OLTMANS, G.A. and HARVEY, J.A. "LH syndrome" and brain catecholamine levels after lesions of the nigrostriatal bundle. Physiology and Behavior 8: 69-78 (1972)

Lesions of the nigrostriatal bundle (NSB), whose fibers pass through the medial portions of the internal capsule and the immediately adjacent lateral hypothalamus (LH), produced a more severe aphagia, adipsia and disturbance of water regulation than did lesions of the medial forebrain bundle (MFB). When deprived of food, animals with NSB lesions drank significantly less than controls and animals with MFB lesions. NSB lesions also produced greater decreases in telenlephalic content of the catecholamines than MFB lesions, while the reverse was true for serotonin. Water intake during food deprivation was highly correlated with telencephalic catecholamine levels in animals with NSB lesions. Thus, the inability to regulate water intake in the absence of food, one of the characteristics and long lasting effects of the LH syndrome appears to be due to destruction of the NSB and the consequent decline in telencephalic content of catecholamines.

PAPESCHI, R. and RANDRUP, A. Catalepsy, sedation and hypothermia induced by alpha-methyl-p-tyrosine in the rat. An ideal tool for screening of drugs active on central catecholaminergic receptors. Pharmakosychiatrie Neuro-Psychopharmakologie 6: 137-156 (1973)

AMT (alpha-methyl-p-tyrosine), injected at 250 mg/kg, ip, at 0 and 3 h in rats, induced a state of reduced exploratory activity and catalepsy, which appeared first at 5-6 h, reached its peak at 10-12 h and was gradually obscured by supervening signs of toxicity of the drug. Aphagia, adipsia and hypothermia accompanied sedation and catalepsy. The behavioral phenomena followed the same temporal pattern as the decrease of concentration of both dopamine and noradrenaline in the whole brain.

Catalepsy and decreased exploratory activity were not consequence of the toxicity of AMT; catalepsy was due to the block of synthesis of dopamine in the CNS, whereas reduced exploratory activity was correlated with that of both central CAs. Adipsia and aphagia could also be related to the central effects of AMT on catecholaminergic neurons.

In contrast, hypothermia appeared to depend mainly on the inhibition of synthesis of both catecholamines in the periphery and of dopamine centrally.

Postural tremor or rigidity were never seen after either AMT or FLA-63.

The fact that catalepsy and sedation appeared only 5-6 h after AMT indicates that spontaneous behavior is not dependent on "newly synthesized" catecholamines, but rather on the total concentration of these compounds in the brain; this concentration must be decreased below a certain critical level before changes of spontaneous behavior set in.

PAUL, S.M., HSU, L.L. and MANDELL, A.J. Extrapineal N - acetyltransferase activity in rat brain. Life Sciences 15(12): 2135-2143 (1973)

An extrapineal enzyme that N-acetylates a variety of indole and catechol alkylamines. including the psychoactive drugs mescaline and d-amphetamine, has been partially purified from rat brain. This enzymatic activity has a distinct pH optimum, is linear with incubation time and protein concentration, and is abolished by heating. Purification is approximately ten fold with ammonium sulfate precipitation and column chromatography, yielding a specific activity of 7936 pmoles of product per mg of protein per hour with tryptamine as substrate.

PIRAINO, A.J. and DiGREGORIO, G.J. Quantitation of barbituates in the induced parotid saliva of rats. The Pharmacologist 16: 217 (19741

QUIMBY, M.W., DOORENBOS, N. J., TURNER, C.E. and MASOUD, A. Mississippi-grown marihuana - Cannabis sativa cultivation and observed morphological variations. Economic Botany 27(1): 117-127 (January-March, 1973)

RANDRUP, A., MUNKVAD, I. and SCHEEL-KRÜGER, J. Mechanisms by which amphetamines produce stereotypy, aggression and other behavioural effects, Proceedings of the Symposia held at the VIII Congress of the Collegium Internationale Neuro-Psychopharmacologicum, Copenhagen, Denmark, August 14-17, 1972. Edited by T. A. Ban, J. R. Boissier, G. J. Gessa, H. Heimann, L. Hollister, H. E. Lehmann. I. Munkvad, H. Steinberg, F. Sulser, A. Sundwall and O. Vinar. Amsterdam, the Netherlands: North-Holland Publishing Company, 1973.

The dopaminergic systems in the forebrain (nucleus caudatus, putamen and some adjacent areas) appear to have effects, in mammals, on many perhaps all types of behaviour, and these effects tend in the extreme to change the whole pattern of behaviour into a stereotyped, apparently aimless one.

At the same time each type of behaviour e.g. locomotion, aggressive and other social activities, drinking etc. appear to be influenced also by other brain systems. The behavioural effects of a drug, which like amphetamines acts on several brain systems (dopaminergic, noradrenergic, serotonergic and possibly others) are therefore bound to be complicated. For example: smaller doses of d-amphetamine cause increase in locomotion of rats while larger doses cause inhibition. The increased locomotion can be stereotyped, consisting in repetition of a fixed route in a restricted part of the cage. Brain dopamine plays a role in these locomotor effects, but locomotion is also influenced by brain noradrenaline.

Recent findings about the mechanisms by which amphetamines produce their behavioural effects are reviewed. Real and apparent contradictions in the most recent publications about experiments with brain lesions are discussed; the extent of lesions in the striatum and the slow recovery of behaviour after such lesions seem to be important items in this context. Clinical implications of the animal experiments are suggested.

RENAULT, P.F., SCHUSTER, C.R., HEINRICH, R. and FREEMAN, D.X. Marihuana: Standardized smoke administration and dose effect curves on heart rate in humans. Science 174: 589-591 (November, 1971)

A spirometer was used to deliver marihuana and placebo smoke to human subjects. This procedure produced linear dose-effect curves on heart rate and replicable dose effects in individual subjects. No differences were observed between experienced and inexperienced smokers in responsiveness to heart rate increases produced by marihuana.

Report of the Panel on the Impact of Information on Drug Use and Misuse. Phase II: Evaluating Drug Information Programs. Washington, D.C.: National Academy of Sciences,. National Research Council, 1973.

ROBINS, L.N. The Vietnam Drug User Returns. Final report submitted to the Special Action Office for Drug Abuse Prevention. Special Action Office Monograph, Series A, Number 2. May 1974. Washington, D.C.: U.S. Government Printing Office, 1974.

Definitive study of the extent and consequences of drug use by Americans in Vietnam. The report also serves as a contribution to the understanding of the natural history of drug abuse.

ROSENBERG, H.C. and OKAMOTO, M. A method for producing maximal pentobarbital dependence in cats: Dependency characteristics. Drug Addiction: Neurobiology and Influences on Behavior, Vol. 3. Edited by J.M. Singh and H. Lal. New York: Stratton Intercontinental Medical Book Company, 1974.

A study is described of a reliable laboratory method for producing pentobarbital physical dependence in the cat. Sodium pentobarbital was administered via a chronically implanted intragastric cannula. Cats were treated 22-40 days, twice a day, with a predetermined dose to produce the maximally tolerable depression of the CNS. Subjective neurological observations were recorded throughout the chronic treatment period. Quantitation of these observations provided a check on our method and showed that the cats were indeed maintained at maximally tolerable doses and that the dose was increased in parallel with the development of tolerance. By 18 hours after abrupt termination of the treatment, signs of withdrawal hyperexcitability appeared. By 24 hours, these signs included tremors, twitching of facial muscles, increased startle response, myoclonic jerking, anorexia, pilo-erection, delirium and grand mal type convulsions. The appearance of these signs was compared to the decline in blood pentobarbital levels. Frequency of grand mal type convulsions was found to be a good Indicator of the degree of dependence. The single most important factor determining the seizure frequency in cats treated by this method was the rate of pentobarbital elimination. The half-life was well correlated with seizure frequency; this indicates that the ability to maintain high levels of pentobarbital between doses, by virtue of differences in elimination rate, played a key role in the determination of the severity of physical dependence.

ROTH, L.J., DIAB, I.M., WATANABE, M. and DINERSTEIN, R.J. A correlative radioautographic, fluorescent, and histochemical technique for cytopharmacology. Molecular Pharmacology 10: 986-998 (1974)

Using mouse intestine, a model system has been developed in which two target cell loci, biogenic amine-containing enterochromaffin cells and regenerating crypt cells, are used for correlation of drug localization with fluorescence and microscope structure. The combined procedure described for the cellular localization of drug and fluorophore is based on the use of frozen freeze-dried sections, dry-mounted on dried photographic emulsion, and has general applicability. Tissues need not be subjected to contact with any solvents until after radioautography, cellular fluorescence, and microspectrophotofluorometry have been completed. The use of freeze-dried frozen sections provides the possibility for localization by immunofluorescence labeling and thus offers the opportunity, by combining radio-autographic and fluorescence labeling to investigate competitive inhibition at the cellular level. Because this technique provides for reversible separation of the tissue from the emulsion for independent treatment, histochemical methods that are potentially destructive for the radioautogram can also be used. The correlative technique described here is rigorously controlled and. systematic, and the results are unambiguous.

SALZMAN, C., VAN DER KOLK, B.A. and SHADER, R.I. Marijuana and hostility in a small group setting. Presented at the American Psychiatric Association Meeting, May, 1975.

SCHMIDT, M.J., ROBISON, G.A. and SCHMIDT, D.E. Cyclic AMP in the rat brain: Microwave irradiation as a means of tissue fixation. Advances in Cyclic Nucleotide Research. New York: Raven Press, 1972. Pp. 425-435.

SCHUBERT, J., NYBACK, H. and SEDVALL, G. Accumulation and disappearance of 3H-tryptophan in mouse brain; effect of LSD-25. European Journal of Pharmacology 10: 215-224 (1970)

3H-Tryptophan was administered intravenously to conscious mice by injection or constant rate infusion. Endogenous tryptophan and 5-hydroxytryptamine levels were not significantly altered by this treatment. 3H-5-HT formed in vivo from the labelled precursor was identified by paper chromatography. Following a pulse-injection of 3H-tryptophan the level of 3H-5-HT in brain rapidly increased reaching a peak within 30 min. Pretreatment of the animals with the tryptophan hydroxylase inhibitor, p-chlorophenylalanine or reserpine, markedly reduced the accumulation of 3H-5-HT.

Following the initial peak, the content of 3H-5-HT declined over several hours at a rate that seemed to be exponential between 30 and 180 min after precursor administration with a half-life of about 60 min. Treatment with p-chloro-phenylalanine 60 min after precursor administration did not accelerate the rate of disappearance of 3H-5-HT indicating that the decline of 3H-5-HT content is predominantly determined by turnover of the amine.

The procedures were used to study the effect of LSD-25 on mouse brain serotonin metabolism. Following LSD-25 treatment the rates of accumulation and disappearance of 3H-5-HT after 3H-tryptophan administration were markedly reduced. The contents of labelled tryptophan and endogenous tryptophan and 5-HT levels were not altered by drug treatment. The results indicate that LSD-25 reduces both synthesis and turnover of 5-HT in brain. The LSD-25 analogue BOL 148 showed no effect on brain 5-HT metabolism. Possible mechanisms of action of LSD-25 are discussed.

SCHUBERT, J., NYBACK. H. and SEDVALL, G. Regional differences in synthesis and turnover of 5-hydroxy-tryptamine formed in vivo from 3H-tryptophan in rat brain. Prag, Czechoslovakia: College of International Neuropsychopharmacology, 1970. P. 391.

3H-Tryptophan was administered i.v. to conscious rats. Rates of accumulation and disappearance of 3H-5-hydroxytryptamine in seven regions of the central nervous system were determined. During infusion of the precursor, 3-H-5-HT accumulated at the highest rate in brain stem, followed by diencephalon, spinal cord, corpus striatum, hippocampus, cerebral cortex and cerebellum. Rates of accumulation of labelled 5-HT were correlated to the regional, distribution of endogenous 5-HT. The disappearance rates of 3H-5-HT from the various brain regions were determined between 60 and 180 min after precursor injection. Treatment with the tryptophan hydroxylase inhibitor, H 22/54, did not alter the rate of 3H-5-HT disappearance. The rate constant for 3H-5-HT disappearance varied about two-fold between regions, and was highest in the brain stem. Assuming that 5-HT in each region is stored in a single compartment the synthesis rate was calculated from the product of the rate constant for 3H-5-HT disappearance and the steady-state level of 5-HT. Rates of 5-HT synthesis were significantly higher in brain stem and diencephalon than in other regions. In corpus striatum, hippocampus and spinal cord synthesis rates were about half that of brain stem. Cerebral cortex and cerebellum synthesized 5-HT at rates that were only 20% and 10% respectively of that in brain stem.

SCHUSTER, C.R. Variables affecting the self-administration of drugs by rhesus monkeys. Use of Nonhuman Primates in Drug Evaluation. Edited by II. Vagtborg. Austin, Texas: University of Texas Press, 1968. Pp. 283-299.

SCHUSTER, C.R. and VILLARREAL, J.E. The experimental analysis of opioid dependence. Psychopharmacology: A Review of Progress, 1957-1967. Edited by D. Efron, J. Cole, J. Levine and J.R. Wittenborn. Washington, D.C.: U.S. Government Printing Office, 1968. Pp. 811-828.

SCHWEITZER, J.W., FRIEDHOFF, A.J., ANGRIST, B.M. and GERSHON, S. Excretion of p-methoxyamphetamine administered to humans. Nature 229: 133-134 (January, 1971)

SEGELMAN, A.B. Cannabis sativa L. (Marijuana). III. The RIM test: A reliable and useful procedure for the detection and identification of marijuana utilizing combined microscopy and thin-layer chromatography. Journal of Chromatography 82: 151-157 (1973)

A simple, reliable and easily performed method for detecting and identifying marijuana in suspect material is presented. The method, designated as the RIM test (Rutgers Identification for Marijuana test), utilizes combined histochemical and thin-layer chromatography techniques and thus eliminates the need for a separate extraction step to obtain a suitable sample for thin-layer chromatographic study.

SELLS, S.B. Evaluation of treatment for drug abuse - A discussion of research problems and approaches from the perspective of the DARP. Report to the Joint NIMH-TCU drug abuse reporting program. The Effectiveness of Drug Abuse Treatment. Edited by S.B. Sells. Evaluation of Treatments, Vol. 1. Washington, D.C.: National Institute of Mental Health, IBR Report 73-14, 1973. Pp. 3-9.

SHEPPARD, C., FIORENTINO, D., COLLINS, L. and MERLIS, S. Performance errors on Ravens Progressive Matrices (1938) by sociopathic and schizotypic personality types. Psychological Reports 23: 1043-1046 (1968)

In an attempt to identify the existence of reasoning errors in psychiatric patients, the performance of male narcotic users defined as sociopathic (N = 36) and schizotypic (N = 34) by MMPI profile patterns was analyzed for avoidable errors on the Ravens Progressive Matrices (RPM). An avoidable error was defined as a failure to solve an item whose difficulty level was within the testee's range of ability as measured by his performance. Construct validity was defined in terms of the intercorrelations of Ravens centile and item difficulty levels. Parametric and non-parametric tests of significance indicated that the schizotypic group commit significantly more identifiable reasoning errors than the sociopathic group.

SHEPPARD, C., RICCA, E., FRACCHIA, J., ROSENBERG, N. and MERLIS, S. Cross-validation of a heroin addiction scale from the Minnesota Multiphasic Personality Inventory. Journal of Psychology 81: 263-268 (1972)

A heroin addiction scale (He) gleaned from MMPI self-report was developed on a sample of 63 prisoner addicts. It was later cross-validated on a sample of 160 prisoner addicts. One purpose of this study was to cross-validate the He scale on a larger sample of male narcotic addicts (N = 274) while extending the use of the scale to this sample drawn from a psychiatric installation. Additionally, attempts were made to evaluate responses of narcotic addicts and two samples of male alcoholic patients (N = 117 and N = 111) on the He scale.

On the basis of the data reported, the following conclusions seem justified. The He scale discriminates heroin addicts from alcoholics in samples treated at psychiatric installations. Whatever the attribute or attributes underlying the He scale, alcoholics and heroin addicts differ in intensity. Heroin addicts score significantly higher. There appears to be possible racial and ethnic response differences on the He scale which indicate the need for further item analyses and refinement of items. But, in view of the incidence and prevalence of drug abuse and addiction in the society, continued reporting of these data seems warranted.

SILVERMAN, I. On the methodology of student drug use surveys: From an epidemiologic to a cybernetic model. Proceedings of the First International Conference on Student Drug Surveys, September 12-15. 1971, Newark, New Jersey. Edited by S. Einstein and S. Allen. Farmingdale, New York: Baywood Publishing Company, 1972. Pp. 195-198.

SILVERMAN, I., BROTMAN, R., SUFFET, F. and ORDES. D. Reaching for accountability in community practice. Public Health Reports 85(3): 251-260 (March, 1970)

SIMON, E.J. Methods used in the study of opiate receptors. Methods in Narcotic Research. Edited by S. Ehrenpreis and A. Neidle. New York: Marcel Dekker, Inc., 1974.

SIMON, E.J. Opiate receptors (methods). Methods in Receptor Research. Edited by M. Blecher. New York: Marcel Dekker, Inc. (in press)

SIMON, E.J., DOLE, W.P. and HILLER. J.M. Coupling of a new, active morphine derivative to sepharose for affinity chromatography. Proceedings of the National Academy of Sciences 69(7): 1835-1837 (July, 1972)

A new, pharmacologically active morphine derivative, 6-succinylmorphine, was synthesized. The properties of this compound and evidence for its structure are presented. Succinylmorphine was covalently coupled to ethylamino-Sepharose. Morphine-Sepharose containing up to 40 mu-g of morphine did not block the electrically stimulated contraction of isolated guinea pig ileum, but after alkaline hydrolysis of beads containing 2 mu-g of morphine the supernatant completely blocked contraction. This block was reversed by the specific morphine antagonist naloxone. Antibodies to morphine were removed from serum by morphine-Sepharose, but not by ethylamino-Sepharose, providing evidence of the efficacy of the beads for affinity chromatography.

SIMPSON, D.D. and SELLS, S.B. Patterns of multiple drug abuse: 1969-1971. International Journal of the Addictions 9(2): 301-314 (1974)

Information concerning types and frequencies of pretreatment drug abuse, obtained by interview from 11,380 patients included in the first two years (June 1969-June 1971) of the NIMH-TCU Drug Abuse Reporting Program, were examined with respect to patterns of usage. Twenty-eight patterns were defined, involving various combinations of drugs used and frequencies of use. The results indicated that the most frequent drug-abuse pattern in this patient sample, accounting for 28% of the entire sample, was the daily or weekly use of heroin with no other drugs. The daily or weekly use of heroin with cocaine, with marihuana, and with both cocaine and marihuana were also frequently observed patterns, and combined with the heroin-only pattern, they characterized the majority of all the patients. The most common patterns reported by the remainder of the patients were of poly-drug use, typically involving marihuana, amphetamines, and barbiturates, as well as heroin and cocaine.

SINGLE, E., KANDEL, D. and JOHNSON, B. The internal validity and reliability of drug use responses in a large scale survey. Journal of Drug Issues (in press)

The problem of developing valid and reliable measures is potentially greater for drug use than for other behaviors because the use of many of the drugs is illegal and disapproved of by society. In the absence of independent criteria, responses to drug use questions may be tested for internal consistency and reliability. In a survey based on a representative, sample of 8. 206 New York State public secondary school students, we find that self-reported illicit drug use is consistent both at one point in time and over time. Further, it is strongly related with adolescents' attributes as well as with data independently obtained from best school friends. Only a very small proportion of respondents report the use of a fictitious drug. Self-reported use of alcohol appears to be less reliable, indicating that for the more socially accepted drugs a higher level of use is necessary to insure accurate recall. Self-reports obtained in large scale surveys appear to provide valid and reliable measures of adolescent illicit drug use.

SMITH, S.G. and DAVIS, W.M. Haloperidol effects on morphine self-administration: Testing for pharmacological modification of the primary reinforcement mechanism. The Psychological Record 23: 215-221 (1973)

Rats were allowed to acquire morphine self-administration behavior and then were extinguished. Following extinction, pre-treatment with saline and saline and various doses of haloperidol were given before a reacquisition test. Reacquisition data indicated that a low dose of haloperidol increased self-administration, while higher doses reduced responding. Data from a second experiment using conditioned reinforcement demonstrated that haloperidol did not block the reinforcing action of morphine. Results are discussed in terms of a need to differentiate between reinforcement antagonism and motor impairment.

SONG, C.H., KANTER, S.L., and HOLLISTER, L.E. Extraction and gas chromatographic quantification of tetrahydrocannabinol from marihuana. Research Communications in Chemical Pathology and Pharmacology 1(3): 375-382 (May, 1970)

Assay of tetrahydronannabinol (THC) and related compounds by gas-liquid chromatography (GLC) has been described by Lerner and Heaysman, et. al. The former prepared methylated derivatives with diazomethane to assure detecting cannabidiolic acid as well as the other common plant cannabinoids. The latter prepared trimethyl silylether (TMSE) derivatives and used a more polar column to effect their separation. Quantitative evaluation could not be made reliably because pure standard was not available. Recently the synthesis of delta-1-trans-THC has been accomplished. This material has been supplied to investigators by the National Institute of Mental Health. A description will be given of simple procedures for extracting THC and related compounds from marihuana plant materials and for quantitative assay of the THC content of such extracts. An evaluation of the stability of extracted THC in ethanol has also been done.

STERNBACH. D.D., ABOOD. L.G. and HOSS, W. A benzilate ester of pyrrolizidine and its stereochemical relationship to other psychotomimetic glycolates. Life Sciences 14: 1847-1856 (1974)

In an effort to further test the hypothesis that psychotomimetic potency is related to the availability of the nonbonding electrons on the N of a series of heterocyclic amino glycolate esters, the 1-benzilate ester of pyrrolizidine was synthesized. The compound was found to have about 1/10 the anticholinergic and central nervous system potency of N-methyl-4-piperidylbenzilate, which was among the most potent centrally active glyc olates. The final product was a racemic mixture and, as determined by nmr, consisted of one diasteroisomer, with the acid moiety trans to the heterocyclic N. By the use of Dreiding models and measurement of the relative rate of quaternization by CH_3I, it was inferred that 1,2-syn interference, by the H's on the adjacent C's, with the nonbonding electrons on N was a factor in the' diminished pharmacological potency of the pyrrolizidine ester.

Student Association for the Study of Hallucinogens, Inc. STASH fact sheet on the British Narcotic System. Grassroots (October, 1972 Supplement)

TAKEMORI, A.E. Determination of pharmacological constants: Use of narcotic antagonists to characterize analgesic receptors. Narcotic Antagonists. Edited by M. Braude, L.S. Harris, E.L. May, J.P. Smith and J.E. Villarreal. Advances in Biochemical Psychopharmacology Vol. 8. New York: Raven Press, 1973.

The concept of pA_x (17) has been used mostly with isolated tissue preparations to identify agonists which act on similar receptors. In recent years our group has applied the concept of pA_x to data obtained in intact animals for the characterization of analgesic receptors. The definition of the apparent pA_2 in vivo then becomes the negative logarithm 01' the molar dose of the injected antagonist which reduces the effect of a double dose of an agonist to that of a single dose. The concentration of the antagonist at the receptor site is unknown but it is assumed to be proportional to the dose. Although pA_2 is regarded as equal to the log of the affinity constant (K_b) of the antagonist for the receptor, this is not entirely true in vivo. However, the "K_b" in vivo should be proportional to the real K_b if the above assumption about the antagonist concentration

Takemori, A.E. continued

is correct. Aside from the theoretical implications of "pA_2" in vivo, the procedure offers a means to summarize a large amount of quantitative data on competitive drug antagonism as well as a standard method to compare antagonists. Our group has used this procedure for the characertization of receptors interacting with narcotic and narcotic-antagonist analgesics, for the comparison of the type of narcotic-receptor interaction involved in various analgesic assays, and for the comparison of the potencies of certain narcotic antagonists, The concept of pA_x has also been used to gather evidence that morphine causes a structural change in analgesic receptors.

TAKEMORI, A.E., STESIN, A.J. and TULUNAY, F.C. A single-dose suppression test in morphine-dependent mice. Proceedings of the Society for Experimental Biology and Medicine 145: 1232-1235 (1974)

A simple single-dose suppression test based on a quantitative method for assessing withdrawal jumping in morphine-dependent mice has been established for the prediction of dependence liability. When various narcotic, non-narcotic and narcotic antagonist agents were coded and tested blindly, the experimenter was able to identify all the drugs correctly.

TART, C.T. On Being Stoned: A Psychological Study of Marijuana Intoxication. Palo Alto, California: Science and Behavior Books, 1971.

TAYLOR, J.F. Methods of chemical analysis. Narcotic Drugs: Biochemical Pharmacology. Edited by D. Clouet New York: Plenum Press, 1971.

TULUNAY, F.C. and TAKEMORI, A.E. Further studies on the alteration of analgesic receptor-antagonist interaction induced by morphine. The Journal of Pharmacology and Experimental Therapeutics 190(3): 401-407 (1974)

In previous studies, we observed that pretreatment of mice with narcotic analgesics induced a substantial increase in the efficacy of narcotic antagonists whereas pretreatment with non-narcotic drugs or antagonists did not. In the present study, experiments were designed to see whether or not there was a relationship between the development of narcotic tolerance and the induction of increased narcotic antagonism. The increase in the efficacy of naloxone due to treatment of animals with morphine is observed before analgesic tolerance can be detected and the efficacy of the antagonist rises much faster than the development of tolerance. The increased efficacy of naloxone reaches a maximum in highly tolerant animals, i.e., those that received a morphine pellet implant for 3 days In the tolerant state, the apparent pA_2 value of morphine-naloxone was 7.82 compared with 6.90 control animals. This represented a greater than 8-fold increase in the apparent affinity constant of the analgesic receptors for the antagonist and indicated that a qualitative rather than a quantitative change in receptors took place with the development of narcotic tolerance. Acute injections of cycloheximide did not alter the ED50 of morphine or the increased potency of naloxone. However, daily injections of cycloheximide for 7 days (4 days prior to morphine pellet implantation and 3 days during the implant) inhibited the development of tolerance by 84% and the increased efficacy of naloxone by 64%. The increased efficacy of naloxone due to treatment with morphine appears to be a sensitive indicator of the development of tolerance.

TULUNAY, F.C. and TAKEMORI, A.E. The increased efficacy of narcotic antagonists induced by various narcotic analgesics. The Journal of Pharmacology and Experimental Therapeutics 190(3): 395-400 (1974)

In a previous study using Nihon Clea (Japan) mice and the abdominal stretching assay, we showed that pretreatment of mice with a single dose of morphine hydrochloride caused a marked increase in the antagonistic effect of naloxone without any apparent change in the analgesic activity of morphine. These results were confirmed using Sasco mice, the tail-flick assay and morphine sulfate. The duration of the increased efficacy of naloxone was greater than 12 and less than 24 hours. Morphine pretreatment induced the antagonistic potency of other antagonists besides naloxone such as nalorphine and diprenorphine. Pretreatment of mice with other narcotic analgesics such as levorphanol and methadone also induced an increased potency of naloxone. On the other hand, pretreatment with the inactive optical isomer of levorphanol, dextrorphan or naloxone itself did not cause this type of change. It is suggested that this increased efficacy of narcotic antagonist due to narcotic pretreatment might be a sensitive indicator of the initiation and development of tolerance to narcotic analgesics.

TURANO, P., CANTON, C., TURNER, W.J. and MERLIS. S. Chromatographic evidence for the existence of 8-hydroxy-chlorpromazine in urine. Agressologie 9(2): 192-194 (March-April, 1968)

TURANO, P., TURNER, W.J. and MANIAN, A.A. Thin-layer chromatography of chlorpromazine metabolites. Attempt to identify each of the metabolites appearing in blood, urine and feces of chronically medicated schizophrenics. Journal of Chromatography 75: 277-293 (1973)

Data are presented for thin-layer chromatographic behavior of chlorpromazine and thirty-five of its metabolites, as well as for the thin-layer chromatographic behavior of forty-two still unidentified metabolites found free or as glucuronides in plasma, erythrocytes, urine or feces. Tables are given on the frequency of occurrence of each compound in each source. The presence and identification of several new phenothiazine metabolites and their methoxylated analogs are reported.

TURNER, C.E. Chemical analysis of cannabis using gas liquid chromatography and thin layer chromatography. Presented at the First South African International Conference on Alcoholism and Drug Dependence, Cape Town, South Africa, November 4-8. 1974.

TURNER, C.E. and HADLEY, K. Preservation of cannabis. Journal of the American Medical Association 223(9): 1043 (1973)

TURNER, C.E. and HADLEY, K. The relationship of chemical analysis to conflicting pharmacological reports on Cannabis sativa L. Committee on Problems of Drug Dependence, Washington, D.C.: National Academy of Sciences. National Research Council, Division of Medical Sciences, 1974.

TURNER, C.E., HADLEY, K.W. and DAVIS, K.H., JR. Constituents of Cannabis sativa L. V. Stability of an analytical sample extracted with chloroform. Acta Pharmaceutics Jugoslavica 23(2): 89-94 (1973)

Chloroform extracts of Cannabis sativa L. are stable under ambient temperature for at least a period of 144 hours. When compared to seven other solvents, chloroform was the solvent of choice for extracting delta-g-tetrahydrocannabinol from plant material. Additionally, chloroform extracts can be used to analyze for other neutral cannabinoids or for their carboxylate acid derivatives.

TURNER, C.E. and MOLE, M.L. Chemical components of Cannabis sativa. Journal of the American Medical Association 225(6): 639 (August, 1973)

TURNER, W.J. and MERLIS. S. Vicissitudes in research: The twenty-four hour urine collection. Clinical Pharmacology and Therapeutics 12(2. Part I): 163-166 (March-April, 1971)

Often much depends in metabolic studies upon the accuracy of 24 hour urine collections. In the belief that many common sources of error occur and lead to faulty conclusions, this report of some experiences in a psychiatric hospital is presented as a cautionary tale. Difficulties described are due to inadequate communication, patient resistance, personnel variables, and medication errors.

TURNER, W.J., TURANO. P.A. and MARCH, J.E. Quantitative determination of chlorpromazine metabolites in urine. Clinical Chemistry 16(11): 916-921 (1970)

A simple, rapid, precise, and accurate method is described for the simultaneous and quantitative determination of conjugated and unconjugated chlorpromazine metabolites in urine. It depends on reduction of sulfoxides to sulfides, and oxidation of sulfides to ion radicals in a solution of $Fe^{+3}(10)^{-3}N$) in 18N H_2S0_4. Absorbance is measured at 422, 530, 565, and 700 nm, and concentration of metabolites in calculated by substituting values obtained in appropriate equations. Our data for urines (from schizophrenic men chronically medicated with chlorpromazine) generally agree with those of other workers.

UYENO, E.T. Lysergic acid diethylamide, chlorpromazine and maze performance. Archives internationes de Pharmacodynamie et de There 184(2): 389-394 (April, 1970)

The effects of LSD-25 and CPZ on the learned performance of eighteen-day old rat weanlings, were evaluated in the two-channel Lashley maze. The time of peak disrupting effect. of LSD-25 was 10 min after the intraperitoneal injection and that of CPZ was 45 min. Dose response experiments, conducted at the time of peak effect, showed that the impairing effects of the compounds were dose-dependent. The median effective dose (ED_{50}) of LSD-25 was 0. 27 mu-mole/kg and that of CPZ was 12.5 mu-moles/ kg. The percentage of LSD-25 treated animals (33.3%) that took more than 50 sec to reach their home cages, was not significantly different from that of CPZ treated animals (21.1%). However, a significantly greater number of LSD-25 treated animals than CPZ treated animals made two or more errors.

VILLARREAL, J.E. A suggested procedure for evaluating the dependence liability of morphine-like compounds with mixed agonist-antagonist properties. Committee on Problems of Drug Dependence. Washington, D.C: National Academy of Sciences, National Research Council, 1969. Pp. 6015-6028.

WAINER, B.H., FITCH. F.W., FRIED, J. and ROTHBERG, R. M. Immunological studies of opioids: Specificities of antibodies against codeine and hydromorphone. Clinical Immunology and Immunopathology 3(2): 155-170 (1974)

Two new immunogenic opioid-protein conjugates were prepared. Codeine-6-hemisuccinate was synthesized from the reaction of codeine with succinic anhydride and hydromorphone-6-carboxymethyloxime was synthesized from the reaction of hydromorphone with alpha-aminoxyacetic acid. Both opioids were attached covalently to bovine serum albumin using the mixed anhydride procedure and employed as immunogens in rabbits. Antibody measured by the ammonium sulfate method showed increases in titer and avidity following subsequent immunizations. The specificities of both antisera were studied by competitively inhibiting the binding of labeled opioid to antibody by the prior addition of increasing concentrations of various unlabeled opioids. The ranges of immunoreactivity of both antisera were different and corresponded closely to the structures of the respective immunizing haptens. These observations suggest that antibodies prepared against codeine, hydromorphonc, and morphine may be used multiply for qualitative as well as quantitative determinations of opioids in biologic fluids.

WAINER, B.H., FITCH, F.W., FRIED, J. and ROTHBERG, R.M. A measurement of the specificities of antibodies to morphine-6-succinyl-BSA by competitive inhibition of ^{14}C-morphine binding. Journal of Immunology 110(3): 667-673 (March, 1973)

Antisera reacting with morphine were produced in rabbits by immunization with morphine-6-succinyl-bovine serum albumin. The antibody assay employed ammonium sulfate precipitation of antibody-^{14}C-morphine complexes. The specificities of the sera were measured by prior incubation of appropriate serum dilutions with increasing concentrations of various unlabeled opioids before the addition of ^{14}C-morphine. Opioids differed in their ability to inhibit interaction of ^{14}C-morphine and antibody; concentrations inhibiting binding of 88 pmol/ml of ^{14}C-morphine by 50% were: morphine-6-hemisuccinate, 0.052 nmol/ml; heroin, 0.10 nmol/ml; morphine, 0.11 nmol/ml; codeine, 0.16 nmol/ml; hydromorphone, 0.50 nmol/ml; nalorphine, 2.1 nmol /ml; meperidine 80.0 nmol/ml; naloxone, 30% inhibition at 1.0 X 10^3 nmol/ml. Variations in the ability to inhibit ^{14}C-morphine binding were related to the nature of the structural dissimilarities between the competing compound and the homologous hapten. Differences in I_{50} values for the opioids studied were reflections of inhibition curves with differing slopes. Such observations allow the possibility of both qualitative and quantitative analyses in assay systems.

WAINER, B.H., FITCH, F.W., ROTHBERG, R.M. and FRIED, J. Morphine-3-succinyl-bovine serum albumin: An immunogenic hapten-protein conjugate. Science 176: 1143-1145 (June, 1972)

Morphine-3-hemisuccinate was synthesized by reaction of morphine with succinic anhydride. This compound was conjugated to bovine serum albumin by the mixed anhydride method, and the degree of conjugation was determined by base hydrolysis of the conjugate, extraction, and measurement of free morphine. An average of 6.5 molecules of morphine were conjugated to each molecule of protein. Eleven rabbits immunized with varying doses of the conjugate were producing antibody 8 weeks later, as determined by a modification of the ammonium sulfate method, which measures primary binding of antigen by antibody.

WAJDA, I.J., MANIGAULT, I., HUDICK. J.P. and LAJTHA, A. Regional and subcrllular distribution of choline acetyltransferase in the brain of normal and morphine treated rats. Federation Proceedings 32(3): 3057 (March, 1973)

Homogenates from the caudate nucleus (CN), cerebral cortex (Cx) and hypothalamus (H) were fractionated, and the distribution of choline acetyltransferase (ChAc) was compared to that of protein, monoamine oxidose (MAO) and potassium. Synaptosomol and mitrochondrial fractions were obtained from discontinuous Ficoll or sucrose gradients. Differences in the distribution of ChAc in the three brain regions were found, and confirmed using continuous sucrose gradients. ChAc was localized in denser particles from CN than from Cx or H. The density of MAO containing particles, however, was similar from all three brain regions. K^+ rich particles coincided with those containing ChAc in Cx and H, but were located in less dense fractions in CN. Morphine treatment, did not influence the distribution of ChAc, but a slight shift of MAO toward lower density fractions was noticed in preparation from CN. Regional differences in the density of cholinergic particles parallel those found in uptake experiments (Green et. al. JPET, 168: 264, 1969). The activation of ChAc by EDTA - butanol medium was also studied. The latent form of ChAc was found to be associated with synaptosomal fractions.

WALLACE, J.E., FARQUHAR. J.K., HAMILTON, H.E. and EVERHART, B.A. Comments on the determination of diphenylhydantoin. Clinical Chemistry 20(4): 515-516 (1974)

WALLACE, J.E., HAMILTON, H.E., BLUM. K. and PETTY, C. Determination of morphine in biologic fluids by electron capture gas-liquid chromatography. Analytical Chemistry 46(14): 2107-2111 (December, 1974)

A method that permits the quantitative determination of morphine at therapeutic levels in 1-2 ml of serum of plasma is described. Morphine levels at less than twenty-five nanograms per ml can be effectively assayed providing an internal standard of nalorphine is employed. Both the opiates are measured by electron capture detection (^{63}Ni) as their respective trifluoroacetyl derivatives. Sensitivity of the technique is sufficient to permit the forensic scientist to establish the cause of death in “opiate sensitivity reactions” as well as those intoxications that involve high blood levels of morphine. The procedure has sufficient reliability for utilization in pharmacokinetic studies of morphine.

WEI, E. Assessment of precipitated abstinence in morphine-dependent rats. Psychopharmacologia 28: 35-44 (1973)

An experimental model is described for quantifying the precipitated abstinence syndrome in morphine-dependent rats. Male rats were made dependent on morphine by subcutaneous implantation of a morphine pellet and the abstinence syndrome precipitated by intraperitoneal injection of naloxone hydrochloride. A ranking system, based on the median effective dose of naloxone for abstinence signs, quantitatively related the incidence of certain precipitated signs to the dose of naloxone. The time course for the development of dependence was shown to be maximal 70–74 h after pellet implantation. Food or water deprivation for 48 h dissociated the body weight loss during abstinence from the behavioral signs of precipitated withdrawal. Ganglionic blockade did not significantly modify abstinence behavior. An evaluative procedure which ranks abstinence signs is proposed for quantifying physical dependence on morphine.

WEI, E. Morphine analgesia, tolerance and physical dependence in the adrenalectomized rat. British Journal of Pharmacology 47(4): 693-699 (April, 1973)

1. Adrenalectomy reduced the median antinociceptive dose (AD50) of morphine in male Sprague-Dawley rats. The antinociceptive effect was assessed by the tail-flick method of D'Amour & Smith (1941).

2. Tolerance to the antinociceptive effect of morphine developed in adrenalectomized and sham-operated rats after chronic exposure to morphine. Development of tolerance did not significantly alter the increased sensitivity of adrenalectomized rats to the antinociceptive effect of morphine.

3. Adrenal weights were not increased in rats rendered physically dependent on morphine by subcutaneous implanation of a morphine pellet. Withdrawal, induced by intraperitoneal injection of naloxone hydrochloride, 4 mg/kg. or by removal of the implanted pellet, resulted in a rapid increase in adrenal weight.

4. In morphine-dependent animals, the incidence of abstinence signs and body weight loss during precipitated withdrawal did not appear to be significantly influenced by adrenalectomy or by corticosterone-pretreatment.

WEI, E., LOH, H.H. and WAY, E.L. Neuroanatomical correlates of morphine dependence. Science 177: 616-617 (August, 1972)

Naloxone hydrochloride, an opioid antagonist, was applied to several discrete brain regions of morphine-dependent rats to precipitate abstinence. Severe withdrawal signs were elicited after administration in the thalamus but not in neocortical, hippocampal, hypothalamic, or tegmental areas of the brain.

WEI, E., LOH, H.H. and WAY, E.L. Neuroanatomical correlates of wet shake behavior in the rat. Life Sciences, 12, Part II: 489-496 (1973)

Immersion of pentobarbital-anesthetized rats into water elicits repetitive shaking movements. These wet shakes are similar to the shaking behavior characteristic of the morphine abstinence syndrome in rats. Morphine sulphate, 10 mg/kg i.p., completely inhibited the wet shake response of normal rats to ice water (2 to 6° C). The inhibitory action of morphine on wet shakes was diminished in rats rendered tolerant to morphine by subcutaneous implantation of a morphine pellet for 3 days. Transverse brain lesions, made bilaterally with an iridectomy knife in anesthetized, non-tolerant rats, completely inhibited the wet shake response to ice water when the transection was made at the mid-collicular level. Lesions at the mid-thalamic level did not significantly affect the wet shake response. It is postulated that the shaking response of morphine abstinence and the wet shake response of normal rats to ice water may share common neural pathways.

WEI, E., LOH, H.H. and WAY, E.L. Quantitative aspects of precipitated abstinence in morphine-dependent rate. The Journal of Pharmacology and Experimental Therapeutics 184(2): 398-403 (1973)

The dose-response relationships of naloxone to selected signs of the precipitated abstinence syndrome were studied in male rats rendered physically dependent on morphine by subcutaneous implantation of two morphine pellets. Abstinence behavior was precipitated by i.p. injection of naloxone hydrochloride 72 hours after the first pellet implant. The median effective dose of naloxone was determined for the quantal abstinence responses of diarrhea, abnormal posturing, ear blanching. ptosis, teeth chattering, swallowing movements, escape attempts and wet shakes. Other signs of precipitated abstinence such as the incidence of seminal emissions and chromodacryorrhea as well as the average number of wet shakes and escape attempts per responding animal were found to exhibit a poor dose-response relationship with increasing naloxone dosage in the tested range of 0.04 to 10 mg/kg. Loss of body weight, measured three hours after naloxone administration, was correlated to the log dose of naloxone. The relative merits of different criteria for quantifying the morphine abstinence syndrome are discussed.

WEI, E. and WAY, E.L. Application of the pellet implantation technique for the assessment of tolerance and physical dependence in the rodent. Methods of Narcotic Research. Edited by S. Ehrenpreis and A. Neidle. New York: Marcel Dekker, Inc., 1974.

WEISS, B. Digital computers in the behavior laboratory. Biomedical Symposium Proceedings. Maynard, Massachusetts: Digital Equipment Corporation Users Society, 1967.

WERNER, I., PETERSON, G.R. and SHUSTER, L. Choline acetyltransferase and acetylcholinesterase in cultured brain cells from chick embryos. Journal of Neurochemistry 18: 141-151 (1971)

Dissociated cells from brains of 7-day chick embryos were grown in primary culture for as long as 20 days. Many of the plated cells grew out long processes. Others, which proliferated rapidly, formed a confluent layer of flat cells after 4-6 days. Total DNA and protein increased five-fold, and activity of choline acetyltransferase (EC2.3.1.6) increased about 40-fold in 20 days. Acetylcholinesterase (EC3.1.1.7) increased three-fold by the fourth day of culture and then declined. The pattern of increase for choline acetyltransferase was similar to that for the in vivo development of the enzyme.

L-Thyroxine, cyclic AMP (adenosine-3',5'-monophosphate) or theophylline promoted increased levels of both enzymes by 30-200 per cent. L-Thyroxine also increased the activity of acetylcholinesterase in vivo by 40 per cent. When overgrowth by flat cells was prevented by the addition of 10^{-3}M-5-flourouracil, there was a decrease in the activity of choline acetyltransferase and an increase in the activity of acetylcholinesterase in comparison to control activities. The addition of 10^{-3}M-morphine or cocaine produced a 30 per cent elevation in the activity of choline acetyltransferase, but this effect could be mimicked with equimolar concentrations of ammonium ion.

WILK, S., GITLOW, S.E. and BERTANI. L.M. Gas liquid chromatographic methods for assay of catecholamine metabolites. Chapter 6 of Methods of Investigative and Diagnostic Endocrinology. Edited by J.E. Rall and I.J. Kopin. New York: North-Holland Publishing Company, 1972.

Highly specific and sensitive techniques have been described for the determination of vanillylmandelic acid, 3-methoxy-4-hydroxyphenylethylene glycol normetanephrine, metanephrine and dopamine by gas-liquid chromatography. With modifications, levels of these compounds may be obtained in tissues, plasma and cerebrospinal fluid as has been accomplished for MHPG. In particular, the utilization of electron capture detection has proven useful in the study of urinary catecholamine metabolites in normal human subjects as well as those with gross derangements in their metabolism due to the presence of neural crest tumors. Moreover, levels of catecholamine metabolites may be adequately evaluated in other states in which only subtle aberrations in autonomic dysfunction are apparent. Future work must be directed toward the development of procedures for norepinephrine and epinephrine in urine and eventually in plasma. Although the potential for sensitive and specific assays of these compounds has been demonstrated technical difficulties arising from derivative instability and sample preparation await solution. Gas-liquid chromatography offers the promise of assay techniques whereby multiple substances perhaps present in only picogram amounts may some day be measured accurately by a single sample preparation from urine, plasma or tissue specimens.

WILSON, T.W., WALLACE, S.C. and McMILLAN, D.E. Morphine drinking as a model of opiate dependence. Presented at the 52nd General Session of the International Association for Dental Research and the Annual Session of The North American Division of IADR. Dental Research (in press)

In an attempt to develop a model for the study of drug abuse patterns, rats were given 0.3 and 1.0 mg/ml solutions of morphine as the only fluid available for 12 days. Initially, both concentrations of morphine decreased fluid intake and disrupted the usual diurnal drinking pattern. All rats drinking the lower-concentration of morphine regained their pre-drug levels of fluid intake in a few days, as did some of the rats drinking the higher concentration. The daily morphine intake was about 50 mg/kg/day (0.3 mg/ml solution) to 120 mg/kg/day (1.0 mg/ml solution). Physical dependence on morphine was demonstrated in the morphine-drinking rats by observations of a variety of abstinence signs following injections of naloxone, or following replacement of the morphine solutions with water. Rats switched from morphine solutions to water, or given naloxone and then switched to water, decreased their fluid intake for 24 hours after morphine was withdrawn and showed a marked decrease in body weight for a week or more. Rats injected with naloxone, but permitted to continue drinking morphine solutions showed a similar pattern of symptoms for a few hours, but then increased their morphine solution intake to terminate the abstinence syndrome.

WINKELHAKE, J.L. and VOSS, E.W., JR. Synthesis, isolation and immunochemical characterization of N-(carboxymethyl-^{3}H)-D-lysergamide. Journal of Labelled Compounds 10(3): 475-488 (July-September, 1974)

Covalent amide linkage of glycine-2-^{3}H to the non-hallucinogenic derivative, d-lysergic acid (LSA). by carbodiimide activation results in a lysergic acid analogue which has potential use in biochemical studies of the mode of action, metabolism and immunology of d-lysergic acid diethylamide (LSD). Optimal conditions for the reaction and isolation of the product, N-(carboxy-methyl-^{3}H)-d-lysergamide. were determined. The product was analyzed by radioimmune assay and by equilibrium dialysis with highly specific antibody to the lysergyl moiety.

WOODLAND, J.H.R., YOLLES, S., BLAKE, D.A., HELRICH. M. and MEYER, F.J. Long-acting delivery systems for narcotic antagonists. Journal of Medicinal Chemistry 16(8): 897-901 (1973)

The relationship between the release rate of cyclazocine from composites with poly(lactic acid) and (a) the molecular weight of the polymer and (b) the form of the composite, as a film sealed in an envelope or as discrete small particles, has been investigated in vivo and in vitro. The release rate is not very sensitive to variations in the molecular weight of the polymer within the values investigated. As may be expected. the lower molecular weight polymer is absorbed faster than the higher molecular weight polymer. The use of the composite as a film sealed in an envelope of pure polymer permits control of the release rate. Desirable delivery rates have been obtained by injecting suspensions of small particles of the composite thereby eliminating the necessity of surgery. In experiments with films, the release rate of cyclazocine in vivo is faster than in vitro, whereas in experiments with small particles a reverse effect is observed.

YANAGITA, T. Development of tolerance and physical dependence to barbiturates in rhesus monkeys. Committee on Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council, 1968. P. 5618.

YANAGITA. T. A technique for self-administration of water insoluble drugs to monkeys by means of chronically implanted stomach catheters. Committee on Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council. 1968. P. 5631.

YANAGITA, T., ANDO, K. and TAKAHASHI, S. A testing method for psychological dependence liability of drugs in monkeys. Committee on Problems of Drug Dependence. Washington D.C.: National Academy of Sciences, National Research Council, 1970. P. 6563.

YOLLES, S., ELDRIDGE. J., LEAFE, T., WOODLAND, J.H.R., BLAKE, D.R. and MEYER. F. Long-acting delivery systems for narcotic antagonists. Controlled Release of Biologically Active Agents. Edited by A.C. Tanquary and R.E. Lacey. New York: Plenum Press, 1974. Pp. 177-193.

YOLLES, S., ELDRIDGE. J.E. and WOODLAND, J.H.R. Sustained delivery of drugs from polymer/drug mixtures. Polymer News 1(4-5): 9-15 (1970)

Experimental measurements have generally confirmed the theoretical predictions of the rate of release of the drug, at least during the first unit of dimensionless time. As yet, our experimental data for the period with theta greater than 1 are not sufficiently reliable to determine whether classical diffusion theory or permeability theory better describes the migration of the drug.

It appears that the method of administering a drug as here proposed will not provide a constant dose rate unless the original concept is modified. There may be many medical situations, of course, where a continuously decreasing dose rate is actually desired. On the other hand, if a nearly constant dose rate is needed, one could leach the impregnated polymer for a brief period just before implantation in the patient. In this way, the concentration of drug near the exposed surfaces of the structure would be reduced. In effect, one would eliminate the early part of the delivery rate curve, where (on a linear plot) the rate drops sharply with increasing time. The rate falls much more gradually Thereafter.

We expect to continue work on this method of administering drugs, developing it to the point where clinical evaluation will be justified.

YUNGER, L. M., HARVEY, J. A. and LORENS, S. A. Dissociation of the analgesic and rewarding effects of brain stimulation in the rat. Physiology and Behavior 10: 909-913 (1973)

Lateral hypothalamic stimulation in rats produces both rewarding and analgesic effects. In comparison to the rewarding effect, significantly higher current intensities were required to produce analgesia as measured by the hot-plate method. The analgesia did not outlast stimulation. Alpha-methyl-p-tyrosine (250 kg/kg) decreased self-stimulation rates but had no effect on stimulation-induced analgesia. It was concluded that the rewarding and analgesic effects of lateral hypothalamic stimulation involve separate neurochemical systems.

ZAKS, A.M., BRUNER, A., FINK, M. and FREEDMAN, A.M. Intravenous diacetylmorphine (heroin) in studies of opiate dependence. Diseases of the Nervous System 30 (Supplement): 89-92 (1969)

II

Drug Chemistry and Metabolism

II. Drug Chemistry and Metabolism

ABEL, E.L., editor. Behavioral and Social Effects of Marijuana. New York: MSS Information Corporation, 1973.

Collection of approximately 32 papers published from 1970-1972 on various aspects of marijuana. Studies on the pharmacology, physiology and pathology of marijuana usage are presented. Specifics discussed are liver function, diabetic coma, growth inhibition, central nervous system metabolism and the chemical identification and synthesis of cannabidiol derivatives. These reports are intended to provide a basis for a chemical understanding of the effects of this widely used drug.

ABRAMS, L.S. and ELLIOTT, H.W. Morphine metabolism in vivo and in vitro by homozygous Gunn rats. The Journal of Pharmacology and Experimental Therapeutics 189(1): 285-292 (1974)

Adult homozygous Gunn and Wistar rats were given daily injections with subcutaneous doses of morphine sulfate starting at 20 mg/kg and gradually increasing to 35 mg/kg over a 30-day treatment period. No differences were found between Gunn and Wistar rats in the average urinary excretion of conjugated morphine during the treatment period. The reported existence of codeine as a urinary morphine metabolite in rats was not confirmed. Incubation of the urine of morphine treated rats with beta-glucuronidase provided no evidence to support the existence of any morphine conjugate other than glucuronide. The percentage of dose recovered as urinary conjugated morphine was not decreased by chronic morphine treatment of either Gunn or Wistar rats but the percentage recovered as free morphine was increased significantly more in Gunn than in Wistar rats. No significant differences were observed between Gunn and Wistar rat uridine diphosphate glucuronyltransferase activity when hepatic microsomes from adult Gunn and Wistar rats were incubated with morphine and uridine diphosphate glucuronic acid. Subsequent hydrolysis of the product with beta-glucuronidase indicated that the morphine conjugate formed was a glucuronide.

ADAMS, T.C., JR. and JONES, L.A. Long-chain hydrocarbons of Cannabis and its smoke. Agricultural and Food Chemistry 21(6): 1129-1131 (November-December, 1973)

A series of long-chain paraffins has been identified in Cannabis and its smoke by gas chromatography and mass spectrometry. The level of hydrocarbons was determined to be about half that found in tobacco and its smoke, although the effect of smoking on the paraffins in the Cannabis plant material was comparable to analogous studies of tobacco and its smoke.

ADAMS, T.C., JR. and JONES, L.A. Phytosterols of Cannabis smoke. Agricultural and Food Chemistry (in press)

The 3-beta-hydroxysterols present in American-grown (MS-13) Cannabis were identified and quantitated in its smoke. The free sterol fraction of the smoke contained campesterol, stigmasterol, and beta-sitosterol in essentially the same ratio as that found in the plant material.

ADLER, F.L., LIU, C-T. AND CATLIN. D.H. Immunological studies on heroin addiction. I. Methodology and application of a hemagglutination inhibition test for detection of morphine. Clinical Immunology and Immunopathology 1: 53-68 (1972)

For abstract, see Section I. Methodology of Drug Research.

ADLER, M.W., KOSTOWSKI, W., RECCHIA. V. and SAMANIN, R. Anatomical specificity as the critical determinant of the effect of raphe lesions on morphine analgesia. European Journal of Pharmacology (in press)

AGHAJANIAN, G.K. and FREEDMAN, D.X. Biochemical and morphological aspects of LSD pharmacology. Psychopharmacology: A Review of Progress 1957-1967. Edited by D. Efron, J. Cole, J. Levine and J.R.W. Henborn. Washington, D.C.: U.S. Government Printing Office, 1968. Pp. 1185-1193.

A brief account is given of some reported effects of lysergic acid diethylamide (LSD) on biochemical systems as well as an analysis of the possible significance of these effects within the context of histochemically defined neuronal systems. The effects of LSD on serotonin metabolism and the binding of serotonin were established and these changes were seen with the psychoactive congeners of the drug. The data show a reduction in serotonin metabolism most marked at the termination of acute behavioral and autonomic effects. The mechanism of the LSD induced changes in the concentration of serotonin and 5-hydroxyindoleacetic acid (5-HIAA) cannot be understood in purely chemical terms since the level of activity of serotoninergic neurons plays an important role in indole metabolism. Whatever the initiating interactions at the biochemical level, the changes in serotonin and 5-HIAA seen after LSD could be secondary to a reduction in the firing rate of the serotoninergic neurons. A number of neural systems related to habituation, to constancies and to maintenance of perceptual and sensory boundaries will have to be identified and studied to elucidate the effects of this class of drugs.

ANGRIST, R., SHOPSIN, B. and GERSHON, S. Metabolites of monoamines in urine and cerebrospinal fluid, after large dose amphetamine administration. Psychopharmacologia 26: 1-9 (1972)

Four physically healthy non-schizophrenic amphetamine abusers volunteered to ingest amphetamine in large doses and to cooperate with behavioral assessments, urine collections and to undergo lumbar punctures before and after doing so. The effects of administered amphetamine on behavior and on urine and cerebrospinal fluid levels of homovanillic acid (HVA), 5-hydroxy indoleacetic acid (5-HIAA), 3-methoxy-4-hydroxy-phenyl glycol (MHPG) and vanillylmandelic acid (VMA) are presented and discussed with regard to the findings of other investigators.

ARREGUI. A., LOGAN, W.J., BENNETT, J.P. and SNYDER, S.H. Specific glycine-accumulating synaptosomes in the spinal cord of rats. Proceedings of the National Academy of Sciences 69(11): 3485-3489 (November, 1972)

Subcellular fractionation of rat spinal cord on continuous sucrose density gradients provides evidence for the existence of a specific synaptosomal fraction (enriched in pinched-off nerve endings) that accumulates glycine selectively by way of a high-affinity transport system. The particles in this fraction sediment to a less-dense portion of sucrose gradients than do particles that accumulate neutral, basic, aromatic, and acidic amino acids. Particles accumulating gamma-aminobutyric acid are even less-dense than those storing exogenous glycine. The glycine-specific synaptosomal fraction also exists in the brain stem but not in the cerebral cortex. These findings provide neurochemical support for the suggestion that glycine has a specialized synaptic function, perhaps as a neurotransmitter, in mammalian spinal cord.

AURORI, K.C. and VESELL, E.S. Comparative stimulatory effects of four phenothiazines on hepatic microsomal enzymes. Drug Metabolism and Disposition 2(6): 566-572 (1974)

Four phenothiazine derivatives were compared with respect to the extent that they stimulated hepatic microsomal drug metabolism of mature male rats. Daily oral administration of chlorpromazine (16 mg/kg) for 3 days stimulated ethylmorphine N-dcmethylase activity to 135% of control values. Three- and seven-day pretreatment with promazine, thioridazine, or triflupromazine, and 7-day pretreatment with chlorpromazine stimulated ethylmorphine N-demethylase activity less than observed for 3-day chlorpromazine pretreatment. Administration of chlorpromazine (32 mg/kg) or of promazine (64 mg/kg) for 3 days stimulated both aniline hydroxylase activity and cytochrome P-450 content to levels exceeding 150% of control values. After 7 days of chlorpromazine or promazine administration, aniline hydroxylase activity declined, whereas cytochrome P-450 content was maintained or increased. After 7 days of pretreatment with thioridazine or triflupromazine, aniline hydroxylase activity and cytochrome P-450 content were weakly stimulated.

BAILEY, D.N. and JATLOW, P.I. Chemical analysis of massive crystalluria following primidone overdose. American Journal of Clinical Pathology 58(5): 583-589 (November, 1972)

A 43-year-old woman was hospitalized with a 36-hr. history of stupor and massive crystalluria following an apparent suicide attempt. Toxicologic studies revealed phenobarbital and primidone in both blood and urine. Collection, purification, and chemical analysis of the urinary crystals are described. Microscopic examination, melting-point studies, infrared and ultraviolet spectroscopy, and thin-layer and gas-liquid chromatography identified the crystals as primidone. The clinical utility of crystalluria in the diagnosis of primidone over-dosage is emphasized.

BAILEY, D. N. and JATLOW, P. I. Methaqualone, a new drug of abuse: Studies of analytical methodology and interpretation of serum drug levels in overdose. Clinical Chemistry 19: 666 (1973)

For abstract, see Section I. Methodology of Drug Research.

BAILEY, D. N. and JATLOW, P. I. Methaqualone overdose: Analytical methodology, and the significance of serum drug concentrations. Clinical Chemistry 19: 615-629 (1973)

For abstract, see Section I. Methodology of Drug Research.

BARTOLINI, A. and DOMINO, E.F. Cholinergic mechanisms in the cat visual system. Federation Proceedings 30: 425 (1971)

The distribution of acetylcholine (ACh), cholineacetylase (ChA), acetylcholinesterase (AChE) and cholinesterase (ChE) were determined in pentobarbital anesthetized cats given 100 mg/kg i.p. physostigmine. The ACh content of discrete brain areas was bioassayed and their enzymatic activity measured using radiochemical techniques. The lateral geniculate and superior colliculus contained high levels of these substances which were as great or greater than those in the caudate nucleus. In contrast, the optic nerve and tract showed very low activity in agreement with previous literature in other species. Five days after bilateral removal of the eyes under pentobarbital anesthesia there was no change in lateral geniculate levels of ACh, ChAc, AChE, and ChE even though it is known that synaptic transmission fails 72-96 hrs after enucleation. This would rule out ACh as the principal synaptic mediator from the retina to the lateral geniculate. Photic stimulation (2.5 flashes/sec for 15 min) did not affect ACh release from the visual cortex of pretrigeminal midpontine cat preparations. The content of ACh in various brain areas showed differential changes following i.p. pentobarbital (40 mg/kg) or scopolamine (1.0 mg/kg). Pentobarbital increased ACh content in all brain areas studied while scopolamine caused a significant decrease in the caudate nucleus and hippocampus but only a slight decrease in the lateral geniculate, superior colliculus and visual cortex.

BASMADJIAN, G.P. and PAUL, A.G. The isolation of an O-methyltransferase from peyote and its role in the biosynthesis of mescaline. Lloydia 34(1): 91-93 (March. 1971)

An O-methyltransferase has been partially purified from Lophophora williamsii and shown to have a molecular weight of 410,000 ± 1000 by Sephadex filtration. This enzyme will transfer the methyl group of S-adenosyl-L-methionine to the meta-hydroxyl group of dopamine and will O-methylate, at various rates, other catecholic and monophenolic phenethylamines that have been postulated as intermediates in the in vivo biosynthesis of mescaline. Naturally occurring phenolic tetrahydroisoquinolines of peyote were not O-methylated.

BEN-ZVI. Z., BERGEN, J.R. and BURSTEIN, S. Cannabinol-7-oic acid: A metabolite of delta-1-tetrahydrocannabinol in the rhesus monkey. Research Communications in Chemical Pathology and Pharmacology 9(1): 201-204 (September, 1974)

Injection of ^{14}C-delta-1-tetrahydrocannabinol (THC) into male rhesus monkeys gave rise to a complex mixture of urinary metabolites. One of these has been isolated and identified as cannabinol-7-oic acid (I). This finding suggests a new metabolic pathway for delta-1-THC and raises the possibility that other cannabinol derivatives may also be formed at earlier stages.

BEN-ZVI, Z. and BURSTEIN. S. 7-oxo-delta-1-tetrahydrocannabinol: A novel metabolite of delta-1-tetrahydrocannabinol. Research Communications in Chemical Pathology and Pharmacology 8(2): 223-229 (June, 1974)

A careful analysis of the incubation products of delta-1-tetrahydrocannabinol (THC) with rat liver microsomes revealed the presence of a hitherto unidentified metabolite. Mass spectral data suggested the 7-oxo derivative; $LiAlH_4$ reduction of this product gave 7-hydroxy-delta-1-tetrahydrocannabinol substantiating this assignment. Such an aldehyde is a likely intermediate in the detoxification of delta-1-THC which leads to acidic products.

BEN-ZVI, Z., MECHOULAM. R. and BURSTEIN, S. Identification through synthesis of an active delta-1(6)-tetrahydrocannabinol metabolite. Journal of the American Chemical Society 92: 3468-3469 (1970)

BEN-ZVI, Z., MECHOULAM, R. and BURSTEIN, S.R. Synthesis of delta-1- and delta-1(6)-tetrahydrocannabinol metabolites. Tetrahedron Letters 51: 4495-4497 (1970)

BEN-ZVI, Z., MECHOULAM. R., EDERY, H. and PORATH, G. 6-beta-delta-1-tetrahydrocannabinol. Synthesis and biological activity. Science 174: 951 (1971)

6-beta-Hydroxy-delta-1-tetrahydrocannabinol, a metabolite of delta-1-tetrahydrocannabinol has been synthesized from delta-1(6)-tetrahydrocannabinol. It shows high tetrahydrocannabinol-type activity in rhesus monkeys. The implications of this finding are discussed.

BERANEK, J.T. Morphine binding by serum globulins from morphine-treated rabbits. Federation Proceedings 33: 474 (1974)

Reports on increased specific morphine binding by serum globulins from heroin addicts have raised questions regarding its significance to tolerance and addiction. Following the lead of Ringle and Herndon, the binding of ^{14}C-morphine-HCl by sera from rabbits variously treated with morphine has been examined by precipitation of bound morphine with ammonium sulfate (0.2 ml serum, 1.3 ml 0.15 M buffer pH 7.3 containing 85 ng = 23,000 cpm labeled morphine-HCl, 1.5 ml sat. ammonium sulfate; ppt. washed twice with 2.5 ml half sat. ammonium sulfate). Pretreatment sera bound an average of 0.2 ng. Among 34 rabbits repeatedly injected SC with solutions of morphine, 3 developed 7-24 fold increases in binding, 16 showed slight increases (max. 4 fold) and the others were negative. In contrast, two implantations of morphine pellets, 8 weeks apart, elicited responses in all of 19 rabbits, ranging from 7-100 fold. Interestingly, rabbits that had previously received injections of morphine solutions showed resistance to this regime in that only one showed a 20 fold rise, 6 showed only slight increases and 3 did not respond at all. The binding protein is concentrated in the globulins precipitable by 1/3 sat. ammonium sulfate. Binding by this fraction persists after peptic digestion and is associated with the fraction containing F(ab')2. The complexes are highly dissociable and the amount morphine bound is proportional to morphine added over a wide range.

BHARGAVA, H.N., AFIFI, A-H. and WAY, E.L. Effect of chemical sympathectomy on morphine antinociception and tolerance development. Biochemical Pharmacology 22: 2769-2772 (1973)

BHARGAVA, H.N. and WAY, E.L. Morphine tolerance, dependence and withdrawal and brain acetylcholine (ACh). The Pharmacologist 16(2): 279 (1974)

Thirty min after administration of morphine sulfate (MS) s.c., doses greater than 20 mg/kg increased brain ACh in male Swiss Webster or ICR mice (20-25 g); however, in male Sprague-Dawley rats (180-220 g), a dose of 40 mg/kg of MS did not alter brain ACh. Mice and rats rendered morphine tolerant-dependent (M) by implantation of 1 and 4 pellets, respectively, for 3 days showed increased brain ACh. Six hr after pellet removel from M mice, this increase was even higher. Brain ACh levels returned to normal beyond 12 hr after abrupt withdrawal. Pellet removal from M rats did not affect brain ACh. Administration of naloxone (N) increased brain ACh in naive mice but decreased in M mice and rats. This decrease in brain ACh in M animals was observed only in those that jumped after N and not in those that failed to jump. The specific activity of brain AChE in jumping and non-jumping mice did not differ. Brain choline levels were unchanged by the above treatments. It appears that N-induced withdrawal jumping in M animals is associated with an enhanced ACh release.

RICHER, J.L. and MECHOULAM, R. Pharmacological effects of two active constituents of marihuana. Archives internationales de Pharmacodynamie et de Therapie 172: 24-30 (1968)

Delta-1(6)-tetrahydrocannabinol was found to possess analgesic properties demonstrable on both mice and rabbits. The mechanism of this action on brain mechanism seems to be different from that of other narcotic analgetic drugs such as morphine, since delta-1(6)-THC lowers the threshold of the arousal response elicited by direct stimulation of the reticular formation and does not revert the blood pressure descend produced by direct stimulation of the sciatic nerve. The potential usefulness of the drug is discussed.

BOLT, A.G. and FORREST, I.S. In vivo and in vitro interactions of chlorpromazine and melanin. Chapter 4 of Recent Advances in Biological Psychiatry, Vol. X. New York: Plenum Press, 1968. Pp. 20-28.

In summary, we postulate that 7-hydroxychlorpromazine and melanoprotein interact in the presence of light in vivo as well as in vitro via a complete charge-transfer reaction. This reaction is considered the basis of the chlorpromazine-induced hyperpigmentation of exposed skin areas in some patients. The fact that this side effect occurs in less than 1% of chronically dosed patients is attributed to elevated levels of circulating unconjugated 7-hydroxychlorpromazine, available for interaction with peripheral melanoprotein, which in turn may also be present in elevated amounts.

BOLT, A.G. and FORREST, I.S. Metabolic studies of chlorpromazine-induced hyperpigmentation of the skin of psychiatric patients. Agressologie 9(2): 201-207 (1968)

BOSIN, T.R., BUCKPITT, A.R. and MAICKEL, R.P. Comparative gas-liquid chromatography of biologically important indoles, and their benzo(beta)thiophene and 1-methylindole analogs. Journal of Chromatography 94: 316-320 (1974)

BOWERS, M.B., JR. Acute psychosis induced by psychotomimetic drug abuse. II. Neurochemical Findings. Archives of General Psychiatry 27: 440-442 (October, 1972)

Following probenecid administration lumbar cerebrospinal fluid 5-hydroxyindoleacetic acid (5HIAA) and homovanillic acid (HVA) were measured before and during phenothiazine treatment in 12 patients who developed psychotic episodes following the ingestion of a psychotomimetic drug, probably D-lysergic acid diethylamide (LSD-25) in all but two cases. Compared to nondrug-induced psychotic patients and inmate controls the drug-induced patients gave evidence of decreased central 5HIAA formation, findings analagous to those obtained following the administration of LSD-like drugs to animals. These results persisted during phenothiazine treatment.

BOWERS, M.B. and ROTH. R.H. Interaction of atropine-like drugs with dopamine-containing neurones in rat brain. British Journal of Pharmacology 44(2): 301-306 (February, 1972)

1. A variety of atropine-like drugs effective in the treatment of drug-induced extrapyramidal syndromes have been investigated with regard to their interaction with dopamine-containing neurones in rat brain.
2. Under some conditions benztropine, trihexyphenidyl, atropine and ethopropazine significantly antagonized the chlorpromazine-induced increase in subcortical concentrations of homovanillic acid.
3. Most of the atropine-like drugs investigated also decreased the turnover of dopamine in the subcortex as measured by following the disappearance of dopamine after administration of alpha-methyl-rho-tyrosine.
4. These findings are suggestive that an imbalance between a dopaminergic and cholinergic system might be closely linked to the pathogenesis of extra-pyramidal movement disorders.

BRAESTRUP, C. Effects of clonidine (catapressan) on synthesis and metabolism of noradrenaline in the central nervous system of rats. Acta Pharmacologica et Toxicologica 35 (Supplement I): 22 (1974)

Recently it was demonstrated that the antihypertensive drug clonidine reduced the endogenous level of 3-methoxy-4-hydroxyplenyleneglycol (MOPEG), a major noradrenaline (NA) metabolite in the CNS (Braestrup, J. Pharm. Pharmac. 1974, 26, 139-141). The observed decrease in MOPEG was further investigated by measuring labelled NA and the two most significant NA-metabolites, MOPEG and 3,4-dihydroxyphenyleneglycol (DOPEG), after intraventricular injection of 3H-dopamine or 3H-tyrosine. Intraventricular injection of 3H-dopamine in clonidine pretreated rats, resulted in an increase to 160 per cent of the controls of 3H-NA accumulation and a decrease to 40 per cent of the controls of both 3H-MOPEG and 3H-DOPEG. Intraventricular injection of 3H-tyrosine resulted in a small decrease in 3H-NA accumulation and a 40-50 per cent decrease in 3H-MOPEG and 3H-DOPEG. These results, obtained on the rat brain in vivo, are in agreement with the contention that clonidine, by an action on central alpha-adrenoceptors, induces a compensatory inhibition of NA -release and also NA -synthesis. The decrease in NA-synthesis apparently is mediated through the tyrosine hydroxylase-step of NA biosynthesis and not. at the dopamine-beta-hydroxylase-step.

BRAESTRUP, C., NIELSEN, M. and SCHEEL-KRÜGER. J. Accumulation and disappearance of noradrenaline and its major metabolites synthesized from intraventricularly injected ^{3}H-dopamine in the rat brain. Journal of Neurochemistry (in press)

BRAESTRUP, C., NIELSEN, M. and SCHEEL-KRÜGER, J. Feed back mechanisms in central noradrenergic neurones in vivo, investigated through changes in noradrenaline metabolism. Journal de Pharmacologie 5 (Supplement II): 11 (1974)

A new technique was applied for the determination of the two major noradenaline (NA) metabolites in the cns of rats, 3-methoxy-4-hydroxyphenylglycol (MOPEG) and 3,4-dihydroxyphenylglycol (DOPEG) mainly in conjugated forms, after intraventricular (IV) injection of tritium labelled dopamine or NA.

Pretreatment with 6-OH-DA IV or reserpine resulted in almost complete inhibition of (3H)NA accumulation after IV injected (3H) dopamine, while the two main NA metabolites were decreased to 15-30% of the control. Intraventricular injection of (3H)NA in 6-OH-DA pretreated rats resulted in a twofold increase in (3H)MOPEG while (3H)DOPEG was unchanged. In contrast reserpine, administered 3 h later than (3H) dopsmine, caused a 175% increase of (3H)DOPEG and only a 50% increase of (3H)MOPEG.

The alpha-adrenoceptor antagonists phenoxybenzamine or aceperone increased (3H)MOPEG and (3H)DOPEG after IV injection of (3H) dopamine, in contrast the levels of both these metabolites were decreased after administration of the alpha-adrenoceptor agonist clonidine.

BRANCHEY, L., BODNER, S. and FRIEDHOFF, A.J. Effect of chronic morphine implantation on tyrosine hydroxylase activity in the rat caudate. Research Communications in Chemical Pathology and Pharmacology 8(4): 707-710 (August, 1974)

Tyrosine hydroxylase (TH) was measured in the caudate of rats implanted with morphine pellets for 3 weeks. During that period the amount of morphine given was increased from 18.7 mg to 225 mg. A control group was implanted with placebo pellets. One day after the last implantation TH activity was found to be significantly decreased in the morphine implanted animals when compared with the controls.

BRAUDE. M.C., MANSAERT, R. and TRUITT, E.B., JR. Some pharmacologic correlates to marihuana use. Seminars in Drug Treatment 1(3): 229-246 (December, 1971)

BROCHMANN-HANSSEN, E. Aspects of chemistry and biosynthesis of opium alkaloids. Pharmacognosy and Phytochemistry. Edited by Wagner and Horhammer. New York: Springer-Verlag, 1970. Pp. 347-369.

BROCHMANN-HANSSEN. E. Opium alkaloids XII: Quantitative determination of morphine in opium by isotope dilution. Journal of Pharmaceutical Sciences 61: 1118-1119 (1972)

For abstract, see Section I. Methodology of Drug Research.

BROCHMANN-HANSSEN, E., CHEN. C.H., CHIANG, H.C., FU, C-C. and NEMOTO, H. Opium alkaloids XIV: Biosynthesis of aporphines--detection of orientaline in opium poppy. Journal of Pharmaceutical Sciences 62(8): 1291-1293 (August, 1973)

For abstract, see Section I. Methodology of Drug Research.

BROCHMANN-HANSSEN, E., FU, C-C. and ZANATI, G. Opium alkaloids IX: Detection of coreximine in papaver somniferum L. based on its biosynthesis from reticuline. Journal of Pharmaceutical Sciences 60(6): 873-876 (June, 1971)

For abstract, see Section I. Methodology of Drug Research.

BROCHMANN-HANSSEN, E., LEUNG, A. T. and RICHTER, W. J. Opium alkaloids XIII. Isolation of 160 hydroxythebaine. Journal of Organic Chemistry 37: 1881 (1972)

For abstract, see Section I. Methodology of Drug Research.

BRONAUGH, R.L. and ERWIN, V.G. Partial purification and characterization of nadph-linked aldehyde reductase from monkey brain. Journal of Neurochemistry 21: 809-815 (1973)

The activity of NADPH-linked aldehyde reductase (EC 1.1.1.2) in various regions of monkey brain was determined in vitro. The highest specific activity of the enzyme was found in areas of the brain stem: including the pons, medulla and midbrain. A greater than 500-fold purification of the monkey brain enzyme was obtained by a combination of ammonium sulphate fractionation and subsequent chromatography on calcium phosphate gel cellulose and DEAE-cellulose. The aldehyde metabolites of the biogenic amines, norepinephrine, serotonin, dopamine and octopamine, were readily reduced by the NADPH-linked aldehyde reductase. The K_m values for 3,4-dihydroxyphenylglycolaldehyde. 3.4-dihydroxyphenylacetaldehyde, and 5-hydroxyindoleacetaldehyde were 12•0 mu-M, 6•1 mu-M, and 27 mu-M, respectively. The maximum velocity (V_{max}) for 3.4-dihydroxyphenylglycolaldehyde was, respectively, five-fold or three-fold greater than that determined for 3,4-dihydroxyphenylacetaldehyde or 5-hydroxyindoleacetaldehyde. The highly purified enzyme derived from monkey brain was markedly inhibited by barbiturates, diphenylhydantoin, and chlorpromazine, but not by pyrazole. From data obtained by sucrose density gradient centrifugation and Sephadex chromatography the molecular weight of aldehyde reductase was determined to be about 70,000 daltons.

BROOKES. L.G. and FORREST, I.S. Chlorpromazine metabolism in sheep. I. In vivo metabolism. Agressologie 12: 245-251 (1973)

In vivo ^{3}H-chlorpromazine metabolism in sheep was followed by urinary and fecal excretion of chlorpromazine and its metabolites. using spectrophotometic thin layer chromatographic and radioquantitation techniques. Placental transfer and passage into the milk and wool were demonstrated for the drug and its metabolites.

BROOKES, L. G. and FORREST, I. S. Inter-species differences in chlorpromazine metabolism in vitro. The Pharmacologist 11(2): 273 (1969)

In vitro metabolism of chlorpromazine has been studied in various mammalian species to provide rapid information on species-specific metabolic pathways for the detoxication of heterocyclic compounds. Hepatic microsomal fractions, conventionally prepared, were incubated with chlorpromazine hydrochloride, previously investigated with regard to its complex biotransformations. Guinea pig, rabbit, cat, dog, squirrel monkey, sheep, ox, pig, sea lion, eland and man were the subjects of qualitative and quantitative studies, with tritium labeled chlorpromazine serving as the substrate for the quantitative work. Apart from the inter-species differences observed in N-oxidation, S-oxidation, mono- and d-demethylation, deamination and hydroxylation, the gradual development of the drug-metabolizing enzyme systems from fetal to adult stages were followed in guinea pig, rabbit and man. Metabolic pathways characteristic of man, were found present in all species except cat and sea lion, which showed a more limited metabolic potential. Accordingly, cat and sea lion were considered suitable model systems for simulation of metabolically handicapped populations such as neonates.

BROOKES, L.G. and FORREST, I.S. Intra-species variation in chlorpromazine metabolism. Research Communications in Chemical Pathology and Pharmacology 5(3): 741-758 (May, 1973)

The in vitro metabolism of chlorpromazine was followed, using hepatic microsomes, from individuals of different ages in man, horse, sea lion, rabbit and guinea pig. In man and horse, the fetal and adult developmental stages were compared, whereas in the sea lion, adults and adolescents were used. In rabbit and guinea pig, the development of pathways for the metabolism of chlorpromazine, was traced from the fetal through adult stages.

In all instances examined, the feti of all species studied, were able to metabolize chlorpromazine in vitro by the pathways of N-oxidation, S-oxidation and mono-demethylation. Di-demethylation and oxidative deamination of the dimethylaminopropyl side chain of chlorpromazine, as well as the ring hydroxylation of the nucleus, were essentially developed postnatally, although prenatal 7-hydroxylation and deamination were observed in a few instances.

Analogous in vivo data were also obtained for man and sheep in neonates and adults, and for rabbit and guinea pig from the fetal through the neonatal to the adult stages.

BROOKES, L.G., HOLMES, M.A., FORREST, I.S., BACON, V.A., DUFFIELD, A.M. and SOLOMON, M.D. Chlorpromazine metabolism in sheep. II. In vitro metabolism and preparation of ^{3}H-7-hydroxychlorpromazine. Agressologie 12: 333-342 (1971)

Sheep liver microsomes incubated with chlorpromazine produced the normal spread of known metabolites of the substrate drug usually seen in vitro. They showed an outstanding capacity for 7-hydroxylation. The fresh microsomal preparations converted from one-third to more than two-thirds of the substrate into various 7-hydroxylated derivatives of chlorpromazine. Manipulation of storage conditions of the microsomal fractions prior to incubation with drug substrate furthermore resulted in the production of nearly 70% of 7-hydroxychlorpromazine, at the expense of other non-phenolic and phenolic metabolites. Thus, in sheep liver microsomes the pathways for 7-hydroxlation were found to be more resistant to deterioration in storage than those for demethylation, N-osidation and sulfoxidation.

BROOKES, L.G., HOLMES, M.A., SERRA, M.T. and FORREST, I.S. Placental transfer of chlorpromazine in rabbits and guinea pigs. Proceedings of the Western Pharmacological Society 13: 127-137 (1970)

Guinea pigs and rabbits, chronically dosed with chlorpromazine throughout their gestation period, were given tracer doses of ^{3}H-chlorpromazine during the last few days of pregnancy. Placental transfer of tracer doses of chlorpromazine in neonatal and fetal animals was studied, and in some instances the tissues of maternal animals were similarly examined for comparison with drug content stored in these tissues. It was concluded from results obtained in 3 litters of guinea pigs and 5 litters of rabbits that from 1 to 4% of the maternal dose was found in the tissues of the litters. Some chlorpromazine metabolites detected in fetal and neonatal tissues, but absent in corresponding placental tissues, may have been produced in utero.

BROWN, D.J., MILLER, F.N., LONGNECKER, D.E., GREENWALD, E.K., HARRIS, P.D. and FORNEY. R.B. The influence of delta-9-tetrahydrocannabinol on cardiovascular and subcutaneous microcirculatory systems in the bat. The Journal of Pharmacology and Experimental Therapeutics 188(3): 624-629 (1974)

Information regarding the cardiovascular and subcutaneous microcirculatory response of delta-9-tetrahydrocannabinol (THC) was obtained by direct observation of the microcirculation in the bat wing, and by blood 'pressure, heart rate and body temperature recordings. An LD50 determination (535 mg/kg i.p.) indicated that doses of 100 and 200 mg/ kg of THC would be well tolerated. These doses produced significant reduction in heart rate and rectal temperature within 30 minutes of THC administration. Blood pressure remained essentially unchanged until 85 minutes after injection. At this time, a significant reduction in blood pressure was obtained with the 200 mg/kg dose. No statistically significant response was noted in the subcutaneous. small artery diameter (30-45 mu) after THC administration. However, small veins (60-90 mu) exhibited significant dilatation within 1 hour after the high dose of THC and remained dilated throughout the experimental period. Early effects on heart rate and rectal temperature indicate rapid i.p. absorption of THC. Latent effects on vein diameter and blood pressure may represent a cause/effect relationship.

BURSTEIN. S. and KUPFER. D. Hydroxylation of trans-delta-1-tetrahydrocannabinol by hepatic microsomal oxygenase. Annals of the New York Academy of Sciences 191: 61 (1971)

BURSTEIN. S., MARTINEZ, J., ROSENFELD. J. and WITTSTRUCK, T. The urinary metabolites of delta-1-THC. The Pharmacology and Experimental Psychology Cannabis and Its Derivatives. London: Oxford University Press, 1972.

BURSTEIN, S. and MECHOULAM, R. Stereospecifically labelled delta-1(6)-tetrahydrocannabinol. Journal of the American Chemical Society 90: 2420 (1968)

BURSTEIN, S., MENEZES, F., WILLIAMSON, E. and MECHOULAM, R. Metabolism of delta-1(6)-tetrahydrocannabinol, an active marihuana constituent. Nature 225: 87-88 (1970)

BURSTEIN, S. and ROSENFELD, J. The isolation and characterization of a major metabolite of delta-1-THC. Acta Pharmaceutics Suecica 8: 699 (1971)

For abstract, see Section I. Methodology of Drug Research.

BURSTEIN, S. and ROSENFELD, J. and WITTSTRUCK. T. Isolation and characterization of two major urinary metabolites of delta-1-tetrahydrocannabinol. Science 176:422-423 (April, 1972)

Two of the major metabolites which appear in rabbit urine after the administration of delta-1-tetrahydrocannabinol have been isolated and their structures have been tentatively established. The available evidence indicates that they are 7-carboxy-delta-1-tetrahydrocannabinols with an additional hydroxyl group on the side chain. The substances occur both free and as conjugates.

BUSH, M. T. and SANDERS-BUSH, E. Phenobarbital, mephobarbital, and methnrbital, and their metabolites. Chemistry and methods for determination. Antiepileptic Drugs. Edited by D. M. Woodbury, J. K. Penry and R. P. Schmidt. New York: Raven Press, 1972. Pp. 293-302.

For abstract, see Section I. Methodology of Drug Research,

BUXBAUM. D.M., YARBROUGH, G.G. and CARTER, M.E. Biogenic amines and narcotic effects. I. Modification of morphine-induced analgesia and motor activity after alteration of cerebral amine levels. The Journal of Pharmacology and Experimental Therapeutics (in press)

CATLIN, D.H., ADLER, F.L. and LIU, C-T. Immunological studies on heroin addiction. II. Applications of a sensitive hemagglutination-inhibition test for detecting morphine to diagnostic problems in chronic heroin addiction. Clinical Immunology and Immunopathology 1(4): 446-455 (1973)

For abstract, see Section I. Methodology of Drug Research.

CAUTHEN, S. E. and KIDD, M. R. Properties of purified azolesterases from rabbit serum. Presented at the American Chemical Society 168th National Meeting. Atlantic City, New Jersey, September 9-13, 1974.

Atropinesterase (E.C. 3.1.1.10) and cocainesterase have been purified 700 and 200-fold respectively from commercially available, pooled rabbit serum. Michaelis constants and pH optima have been determined for atropineesterase using (-)-hyoscyamine and (-)-hyoscine as substrates and for cocainesterase using cocaine and tropacocaine as substrates. Studies using other substrates have been done with purified fractions of the enzymes in attempts to clarify conflicting reports in the literature concerning subsrate specificities. The effects on atropinesterase antivity of altering configuration around the alcohol bearing carbon atom in the tropine ring and altering substituents on the bridge nitrogen atom in the substrate will be discussed. Data regarding relative activities of cocain-esterase with respect to the two ester functions in the substrate will be presented. Isozymes of the two enzymes have been reported in electrophoresis studies of both atropinesterase and cocainesterase from crude rabbit serum; zymograms of purified fractions using polyacrylamide gel electrophoresis will be presented.

CAUTHEN, S. W., KIDD, M. R. and LARRISON, S. B. Substrate concentration and ionic strength activation of partially purified atropinesterase. Presented at the American Chemical Society 27th Southwest Regional Meeting, San Antonio, Texas, December 1-3, 1971.

Atropinesterase (EC 3.1.1.10) was fractionated from commercially available, pooled rabbit serum. It has been studied with respect to heretofore unreported, but physiologically significant, substrates; its properties regarding cation requirements have been studied with atropine as substrate. The following methods have thus far been worked out for enzyme purification: Ammonium sulfate fractionation followed by dialysis, gel filtration (Sephadex G-200) eluted with potassium phosphate buffer (0.002M, pH 7.0) and chromatography on DEAE-Sephadex A-50 using a linear gradient from 0.1 to 0.4N KCl in phosphate buffer followed by diafiltration on Amicon membrane UM-20E. The ability of the fractionated enzyme to catalyze the hydrolysi of new substrates, cocaine hydrochloride, atropine methyl nitrate, scopolamine hydrohromide, homatropine hydrobromide, hyoscyamine hydrobromide and homatropine methyl bromide, was found to be comparable to that observed with atropine as substrate, except when the methylated alkaloids were substrates. Substrate concentration related to activation by monovalent cations was examined using atropine sulfate.

CHATTERJIE, N., FUJIMOTO, J.M., INTURRISI, C.E., ROERIG. S., WANG, R.I.H., BOWEN. D.V., FIELD. F.H. and CLARKE, D.D. Isolation and stereochemical identification of a metabolite of naltrexone from human urine. Drug Metabolism and Disposition 2(5): 401-405 (1974)

For abstract, see Section I. Methodology of Drug Research.

CHATTERJIE, N., INTURRISI, C.E., FUJIMOTO, J.M. and ROERIG, S. Species variation in the stereochemistry of a metabolite of naltrexone. The Pharmacologist 16(2) (Fall, 1974)

For abstract, see Section I. Methodology of Drug Research.

CHEN, H. and DAVIS, F.F. Identification of 14-hydroxy morphine as a microbiological transformation product of morphine. Journal of Chromatography (in press)

CHENEY, D.L. and GOLDSTEIN, A. The effect of rho-chlorophenylalanine on opiate-induced running, analgesia, tolerance and physical dependence in mice. The Journal of Pharmacology and Experimental Therapeutics 177(1): 309-315 (1971)

Daily i.p. administration of rho-chlorophenylalanine (PCPA) (320 mg/kg), which lowered brain serotonin to 34% of its normal level within three days, failed to inhibit the development of tolerance to opiate-induced running activity or analgesia. Under these same conditions, PCPA had no effect upon the development of physical dependence. Levorphanol-induced running was potentiated by PCPA and inhibited when scrotonin levels were restored by administration of 5-hydrosytryptophan, even in the presence of PCPA. PCPA treatment caused neither potentiation nor inhibition of levorphanol-induced analgesia.

CHENEY, D.L., GOLDSTEIN, A., ALGERI. S. and COSTA, E. Narcotic tolerance and dependence: Lack of relationship with brain serotonin turnover. Science 171: 1169 (1971)

Serotonin turnover was measured in mouse brain by means of the conversion of radioactivity from labeled tryptophan into serotonin. Animals with a high degree of tolerance to and physical dependence on morphine did not differ from control mice.

CHENEY, D.L., GOLDSTEIN, A. and SHEEHAN, P. Rate of development and reversibility of brain tolerance and physical dependence in mice treated with opiates. Federation Proceedings 29(2): 685 (March-April, 1970)

Previous work (J. Pharmacol. Exp. Ther. 169: 175, 1969) was concerned with tolerance in the whole animal, without regard to separate contributions of metabolic and brain components. Now we have determined relationships between dose, blood level, brain level, and running activity (a measure of opiate action)--all at different stages in development of tolerance. Tolerance was induced by injections of levorphanol or implantation of morphine pellets. Onset and disappearance of physical dependence was estimated by using naloxone to precipitate the jumping syndrome characteristic of opiate withdrawal in mice.

Our results indicate that a significant part of tolerance, which has a rapid onset, is accounted for by faster conjugation and excretion. Brain tolerance develops more slowly. It is reversible. Its rate of onset, like that of metabolic tolerance, is a function of the concentrations of opiate to which the animal is exposed and the frequency of such exposures. The same description applies to development and disappearance of the process in brain that is responsible for physical dependence. Continuous treatment with rho-chlorophenylalanine (320 mg/kg) starting 3 days prior to morphine pellet implantation failed to block development of physical dependence.

CHENOWETH, M. B., DOMINO, E. F. and VAN DYKE, R. A. The distribution and metabolism of volatile anaesthetic agents. Fourth World Congress of International Anesthesia, 1939. Pp. 382-387.

It develops that the 'non-metabolized, stable central nervous system depressants' we use as anaesthetics are actually much metabolized, not particularly stable, and show a remarkable predilection to accumulate preferentially in places other than the brain.

CICERO, T.J., MEYER, E. R. and SMITHLOFF, B.R. Alpha adrenergic blocking agents: Antinociceptive activity and enhancement of morphine-induced analgesia. The Journal of Pharmacology and Experimental Therapeutics 189(1): 72-82 (April, 1974)

The effects of reducing the activity of norepinephrine in the nervous system, either by depleting endogenous levels via dopamine-beta-hydroxylase inhibition or by blocking its effects at the receptor level, on hot plate reaction time and on morphine's analgesic activity, were determined in rats. Inhibition of dopamine-beta-hydroxylase resulted in a significant prolongation of morphine's antinociceptive activity on the hot plate. The alpha adrenergic blocker, phenoxybenzamine, alone nearly doubled reaction time on the hot plate when 10 mg/kg were administered prior to testing. The effect of a minimally effective dose of morphine on hot plate reaction time was significantly enhanced, both in the initial increase in reaction time after the administration of the narcotic and the duration of its antinociceptive activity. The combined effect of phenoxybenzamine and morphine on hot plate reaction time was substantially greater than predicted on the basis of addition of the 2 drugs' effects. Another alpha blocker, phentolamine, also produced a slight degree of antinociceptive activity by itself and an enhancement of morphine induced analgesia, whereas 2 beta adrenergic blockers, propranolol and practolol, were ineffective. The observed interaction between phenoxybenzamine and morphine was not related to altered distribution of the narcotic in the brain. Results of these studies suggest that the action of morphine and related narcotics may be associated with a reduction in norepinephrine's activity in the nervous system particularly at alpha adrenergic receptor sites.

CICERO, T.J., SHARPE, L.G., ROBINS. E. and GROTE, S.S. Regional distribution of tyrosine hydroxylase in rat brain. Journal of Neurochemistry 19: 2241-2243 (1972)

The rate-limiting step in the biosynthesis of the catecholamines is the conversion of L-tyrosine to L-3,4-dihydroxyphenylalanine (DOPA). a reaction catalysed by tyrosine hydroxylase (EC = 1.14.3.2) (Levitt, Spector, Sjoerdsma and Udenfriend, 1965). Although the chemical properties of tyrosine hydroxylase have been extensively examined (Nagatsu, Levitt and Udenfriend, 1964a; Petrack, Sheppy and Fetzer, 1968; Nagatsu, Sudo and Nagatsu, 1971), there have been few reports on its distribution in brain. In the present study, we have examined the regional distribution of tyrosine hydroxylase in the rat brain.

CICERO, T.J., SHARPE, L.G., WILCOX, C.E. and SMITHLOFF, B.R. Effects of morphine in vivo and in vitro on tyrosine hydroxylase activity in rat brain. The Journal of Pharmacology and Experimental Therapeutics (in press)

CICERO, T.J., WILCOX, C.E., SMITHLOFF, B.R., MEYER, E.R. and SHARPE, L.G. Effects of morphine, in vitro and in vivo, on tyrosine hydroxylase activity in rat brain. Biochemical Pharmacology 22(24): 3237-3246 (December, 1973)

The effect of morphine on the synthesis of catecholamines was determined in rat brain. Morphine produced a dose dependent increase in the biosynthesis of the catecholamines. To assess whether morphine might enhance the synthesis of norepinephrine and dopamine by a direct chemical interaction with tyrosine hydroxylase, the rate limiting step in their biosynthesis, the effects of the narcotic on the activity of the enzyme were determined in several regions of rat brain. The effects of morphine treatment, in vivo, on enzyme activity were also examined. The results of these studies indicated that acute injections of morphine had no effect on tyrosine hydroxylase activity, in vitro, indicating that the drug did not alter the level of an endogenous activator or inhibitor of tyrosine hydroxylase. Further studies indicated that development of tolerance to and physical dependence on morphine was not associated with an increase in the activity of brain tyrosine hydroxylase activity. The results suggest that morphine does not enhance the biosynthesis of catecholamines by a direct effect of tyrosine hydroxylase and that tolerance to the narcotic is not characterized by an induction of this enzyme.

CLINESCHMIDT, B.V. and HORITA, A. The monoamine oxidase catalyzed degradation of phenelzine-1-^{14}C, an irreversible inhibitor of monoamine oxidase--I. Studies in vitro. Biochemical Pharmacology 18: 1011-1020 (1969)

Exposure of phenelzine-1-^{14}C to a biotransformation system which included mitochondria isolated from homogenate of rat liver resulted in a metabolite with thinlayer chromatographic characteristics identical to those of authentic phenylacetic-1-^{14}C acid.

The conversion of phenelzine to phenylacetic acid was found to be: (1) relatively insensitive to preincubation of the bioconversion system with cyanide; (2) dependent upon the presence of O_2; (3) abolishing by boiling the mitochondrial component of the system; and (4) inhibited by preincubation of the biotransformation system with isocarboxazid, pheniprazine, tranylcypromine or pargyline.

These results provide the first substantial evidence for an irreversible inhibitor of monoamine oxidase (MAO) acting as a substrate of the enzyme, and the results suggest that degradation of the inhibitor is very likely accomplished by oxidative dehydrazination, a reaction mechanism previously unknown for MAO.

CLINESCHMIDT, B.V. and HORITA. A. The monoamine oxidase catalyzed degradation of phenelzine-1-^{14}C, an irreversible inhibitor or monoamine oxidase--II. Studies in vivo. Biochemical Pharmacology 18: 1021-1028 (1969)

Rats receiving approx. 2.5 mg/kg of phenelzine-1-^{14}C by the intraperitoneal route were placed in metabolism cages and their urine collected for 24 hr. Phenylacetic-1-^{14}C acid was recovered as a major metabolite.

Pretreatment of the animals with tranylcypromine (10 mg/kg) or pargyline (100 mg/kg) prior to injection of radioactive phenelzine markedly reduced the urinary excretion of phenylacetic-1-^{14}C acid and the excretion of other unidentified metabolites appeared to increase. Inhibition of monoamine oxidase (MAO) with tranylcypromine or pargyline had no effect on the urinary excretion of an equimolar dose of phenylacetic-1-^{14}C acid administered by the same route. Therefore, pretreatment of rats with tranylcypromine or pargyline appears to

Clineschmidt, B.V. and Horita, A. The monoamine - II. . . continued
have decreased the bioconversion of the injected phenelzine to phenylacetic acid. These results provide further evidence that phenelzine, in addition to being an irreversible inhibitor, is also a substrate of MAO in the intact animal.

CLONINGER, C.R., PACKMAN, P.M., CICERO, T.J., BOSHANS, R.L. and ROBINS, E. Morphine dependence and enzyme activity in the h,ypothalamus. Biochemical Pharmacology 23(5): 983-988 (March, 1974)

Tolerance to and physical dependence on morphine were produced in rats by the implantation of morphine pellets. When both reached peak levels, the rats were sacrificed and malic dehydrogenase, lactic dehydrogenase and glucose-6-phosphate dehydrogenase were measured by sensitive microchemical methods in 8 hypothalamic nuclei and in the cortex, cerebellum and liver. In the medial portion of the ventromedial nucleus of the hypothalamus, glucose-6-phosphate dehydrogenase was 20 percent lower in the morphine dependent animals than in the controls. This was the only significant change detected for any of the 3 dehydrogenases in any of the regions or organs examined. The data indicate that chronic morphine administration does not produce a generalized change in the activity of major metabolic pathways in either the brain or liver. The regionally selective effect on glucose-6-phosphate dehydrogenase activity may reflect an involvement of the ventromedial hypothalamus in at least some aspects of the development of tolerance and physical dependence on narcotics.

CLOUET, D.H. Cellular biochemistry of narcotic analgesic drugs in the central nervous system of the rat. Psychiatric Quarterly 46(3): 384-392 (1972)

Research on the effects of opioids on the biosynthesis, storage, release, and catabolism of neurotransmitters at the nerve ending and the effects of drugs on the structure of the nerve ending and its component macromolecules is reviewed.

CLOUET, D.H. Effect of morphine on protein and ribonucleic acid metabolism in brain. Drug Abuse: Social and Psychopharmacological Aspects. Edited by J. Cole. Springfield, Illinois: Charles C. Thomas, 1969. Pp. 153-163.

The metabolism of protein and ribonucleic acid (RNA) in rat brain was examined after the administration of morphine to the animals. Experiments showed that a single dose of morphine produced profound changes in overall protein and RNA synthesis in the brain. The inhibition of protein synthesis. as measured both in vivo and in vitro, may be related to a decrease in polyribosomal activity in promoting amino acid incorporation into protein and a decrease in the stability of ribosomes in the polysomal structure. The apparent inhibition of RNA turnover in the brains of morphine treated rats is due to changes in precursor pool size, and the true situation is more likely to be that seen in the labeling patterns in which RNA synthesis is increased in nuclear fractions from morphine treated animals. There is little evidence of whether these changes in protein and RNA synthesis in brains of morphine treated rats are basic phenomena or secondary to changes in other biochemical systems. The changes in pool size of labeled amino acids and orotic acid in treated animals suggest that such phenomena as oxidative metabolism or transport may also be involved in the biochemical response to narcotic drugs.

CLOUET, D.H. The effects of drugs an protein synthesis in the nervous system. Protein Metabolism of the Nervous System. Edited by A. Lajtha. New York: Plenum Press, 1970. Pp. 699-713.

The effects which drugs have on protein synthesis in the nervous system of experimental animals fall into two general categories: (1) effects similar to those produced in other tissues by drugs which are well known as metabolic inhibitors or antibiotics, and (2) effects produced by drugs which have the nervous system as their probable site of action and which thus may be expected to have specific effects on metabolism in nervous tissue. In the present discussion the effects of metabolic inhibitors, antibiotics, and other, presumably nonspecific, drugs on protein synthesis or turnover in brain and nerve will be described briefly, with examples cited from the literature. Another class of drugs, those which affect a single enzyme system or classes of enzymes, which can be considered to be affecting a portion of the protein of the nervous system, will be discussed in terms of representative studies. Major attention will be given to studies from this laboratory on the responses in nervous tissue to the administration or addition of narcotic analgesic drugs.

CLOUET, D.H., editor. Narcotic Drugs: Biochemical Pharmacology. New York: Plenum Press, 1971.

Collection of articles by various authors concerning the chemistry of narcotic analgesic drugs, the metabolic disposition of narcotic analgesic drugs, metabolic effects, sites of action, and tolerance and dependence. Additionally, studies in man regarding the electrophysiological properties and the pharmacologically based therapeutic programs are discussed.

CLOUET, D.H. Protein and nucleic acid metabolism. Chapter 9 of Narcotic Drugs: Biochemical Pharmacology. Edited by D.H. Clouet. New York: Plenum Press, 1971. Pp. 216-228.

CLOUET, D.H., JOHNSON, J.C., RATNER, M., WILLIAMS, N. and GOLD, G.J. The effect of morphine on rat brain catecholamines: Turnover in vivo and uptake in isolated synaptosomes. Journal of Neurochemistry (in press)

CLOUET, D.H. and NEIDLE, A. The effect of morphine on the transport and metabolism of intracisternally-injected leucine in the rat. Journal of Neurochemistry 17: 1069-1074 (July, 1970)

Intracisternally injected L or D-(^{14}C)leucine was retained longer in the brains of morphine-treated rats than in saline-injected control animals. This resulted in higher levels of the labelled leucine and of labelled metabolites of the L-isomer in free pools of brain tissue. However, the absolute levels of brain amino acids and the relative distribution of radioactivity among L-leucine metaboliles in brain were unaffected by treatment with morphine, indicating that no disturbance of leucine oxidation through the citric acid cycle was produced by the drug. The inhibition of protein synthesis caused by acute administration of morphine was calculated to be greater than previously reported since morphine treatment increased the specific radioactivity of the free pool of leucine in brain following the intracisternal injection of the labelled amino acid. Possible mechanisms responsible for these morphine effects are discussed.

CLOUET, D.H. and RATNER. M. The biosynthesis of catecholamines in the brains of morphine treated rats. Committee on Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council, 1970. P. 7025.

CLOUET, D.H. and RATNER, M. Catecholamine biosynthesis in the brains of morphine-treated rats. Science 168: 854-856 (May. 1970)

In the brains of rats without tolerance to morphine, the accumulation of (^{14}C)dopamine formed from (^{14}C)tyrosine injected intracisternally is increased, reaching a maximum in the hypothalamus and striatum 1 hour after administration of morphine. In tolerant rats, the rate of incorporation of carbon-14 into dopamine and into norepinephrine in these areas is more than twice that in animals that have received only one injection of morphine.

CLOUET, D.H. and RATNER. M. Effect of morphine on brain tyrosine hydroxylase activity. Federation Proceedings 30: 501 (1971)

A partially purified tyrosine hydroxylase was prepared from homogenates of six areas of rat brain and the activity was measured with 3,5 diH^3-tyrosine as substrate. The enzyme activity was above control in only one treatment group of rats receiving morphine either by injection or by pellet implantation: in the hypothalamus, striatum and midbrain of rat receiving a morphine pellet plus daily injections of morphine for ten days. On other regimens of drug administration the enzyme activity was unchanged or lower than control in these areas and in the other areas of brain. It is possible, however, that the assay for tyrosine hydroxylase activity in purified preparations did not reflect the catecholamine synthetic capacity in vivo as tyrosine hydroxylase activity was found to vary biphasicall when catecholamines or narcotic drugs were added in concentrations from 10^{-3} to 10^{-5} M to the brain homogenates before the enzyme was isolated for assay. Since administration of morphine is known to alter brain catecholamine levels and to result in drug uptake into brain, it is possible that the redistribution of these compounds during tissue homogenization might effect enzyme activity measured in vitro. In the tyrosine hydroxylase assay itself, the addition of not only dopa, dopamine or norepinephrine, but also morphine, methadone or levorphanol altered the enzyme activity.

CLOUET. D.H. and RATNER. M. Tyrosine hydroxylase activity in areas of the brains of morphine-treated rats. Committee on Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council, 1971, P. 728.

In most animal species the admin. of morphine produces a release and subsequent depletion of brain catecholamines in the central nervous system. In animals chronically treated with morphine, this depletion does not occur. Instead, there is either no change or an increase in the levels of brain catecholamines. Earlier studies from this laboratory have indicated that the rate of in vivo synthesis of catecholamines in some areas of rat brain is affected by the admin. of morphine. We found an increased synthesis of dopamine in the hypothalamus and striatum of animals injected with morphine one hour prior to sacrifice, and an even greater increase in the same areas after the fifth daily injection of the drug. Since the rate of biosynthesis of catecholamines depends on the activity of the first enzyme in the biosynthesis pathway, tyrosine hydroxylase, this enzyme was assayed in various areas of the brains of morphine-treated rats.

CLOUET, D.H. and WILLIAMS, N. The binding of narcotic analgesics in synaptosomal and other particulate fractions. The Pharmacologist 13: 313 (1971)

Narcotic analgesics are localized in the synaptosomal fraction (NEP) of rat brain after incubation of rat brain homogenate with drug in vitro and in vivo after injection of the drug in analgesic doses to rats. When radiolabeled meperidine, methadone, etorphine, morphine or dihydromorphine (DHM) are incubated at 10^{-5} M concentration with brain homogenates prior to density gradient centrifugation, the uptake is 24.8, 7.1. 6.3, 3. 7 and 2.6%, respectively. The extent of the binding and the exact localization in the gradient is dependent on pH and divalent ions, e.g. the uptake of methadone at pH 7.2 is decreased from 58% to 16% in 0.01 M $CaCl_2$ and increased to 68% in 0.005 M EDTA. At pH 6, the particulate uptake of methadone is 37% localized in one peak at 0.8 M sucrose and at pH 7.2 is 58% with a large peak at 0.8 M and a smaller one at 1.0 M sucrose in the NEP. Both peaks lose labeled drug when the crude mitochondrial fraction is ruptured before centrifugation. Similarly, DHM is lost from a single peak at 1.0 M sucrose after disruption of the NEP. After its injection, H^3-DHM is found in the same NEP fraction and is lost by osmotic shock of the NEP. Neither the localization of DHM in the NEP, nor its loss on particle rupture is reversed by the administration of antagonists or by tolerance.

CLOUET, D.H. and WILLIAMS, N. The effect of narcotic analgesic drugs on the uptake and release of neurotransmitters in isolated synaptosomes. The Journal of Pharmacology and Experimental Therapeutics 188(2): 419-428 (February, 1974)

The effect of morphine and other narcotic analgesic drugs on the uptake and release of neurotransmitters in nerve ending preparations isolated from rat brain was studied. The uptake of carbon-14-dopamine into rat striatal synaptosomes and of carbon-14-norepinephrine into hypothalamic synaptosomes was inhibited by morphine. Kinetic analyses of dopamine uptake in the presence of morphine suggested that low affinity uptake was inhibited rather than high affinity uptake. Narcotic drugs had no direct effect on catecholamine release. The release of carbon-14-acetylcholine from carbon-14-choline precharged striatal synaptosomes was inhibited by morphine. The intrasynaptosomal synthesis of carbon-14-acetylcholine from carbon-14-choline was also inhibited by the same concentration of morphine. Other opioids also inhibited the release of newly synthesized carbon-14-acetylcholine from striatal synaptosomes. Levorphanol inhibited carbon-14-acetylcholine release, while its less active isomer, dextrorphan, did not inhibit release, thus separating the effects of narcotic agonists by activity. However, another pair of isomers, levo- and dextro-methadone, were almost equally active as inhibitors of acetylcholine release from striatal nerve ending preparations.

CLOUET, D.H. and WILLIAMS, N. Localization in brain particulate fractions of narcotic analgesic drugs administered intracisternally to rats. Biochemical Pharmacology 22: 1283-1293 (1973)

Radio-labeled dihydromorphine, morphine, methadone and levorphanol were administered to rats in pharmacologically active doses by the intracisternal route of administration, and the rats were killed 0.5 or 1 hr later. The drugs were localized in the fraction of brain containing the pinched-off presynaptic nerve-endings, the synaptosomes. as well as in the soluble portion of the tissue. The ^{14}C-labeled narcotic antagonists, naloxone and nalorphine, were also localized in the same particulate fraction of brain. The amount of drug in the synaptosomal fraction was dependent on the dose of drug, on the time between drug administration and sacrifice, and on the region of brain, and was specific for each narcotic agonist and antagonist. The relevance of this localization of narcotic analgesic drugs in the synaptosomal fractions of rat brain to the mechanism of action of the drugs remains to be explored.

COCHIN, J., SPIVAK, C. T. and LIPPER, S. Characteristics of the inhibition of N-demethylation of narcotic drug substrates by various antagonists. The Pharmacologist 9: 218 (1967)

Previous studies by a number of workers [J. Pharmacol. 121, 107 (1957); J. Med, Chem. 6, 237 (1963)] described the inhibition of morphine N-demethylation by nalorphine as a non-competitive or mixed type. Certain aspects of the activity of nalorphine as an in vivo antagonist led us to reexamine the nature of its in vitro action. Using concentrations of nalorphine similar to those in previous studies (1.0 and 2.0 x 10^{-4}M), the inhibition of morphine N-demethylase was found to be of a mixed type However, with lower concentrations of inhibitor, (0.33, 0. 50 and 0.67 x 10^{-4} M) the inhibition is competitive. The same kinetics were observed with naloxone and levallorphan. The inhibition of demethylation of oxymorphone by all three inhibitors was competitive even at higher concentrations (up to 2.0 x 10^{-4}M). With meperidine as the substrate, nalorphine proved to be a very weak inhibitor at the low concentrations at which it was quite effective with other substrates, and inhibited competitively at higher concentrations. The results seem to support the hypothesis that narcotic drugs and their antagonists compete for the same enzyme and receptor sites.

COHN, R.A., WILLIAMS, B.J., NASH, I.B. and PIRCH, J.H. Distribution of ^{14}C-delta-9-THC in male and female rats. The Pharmacologist 16: 260 (1974)

Previous studies, utilizing a behavior rating technique (Proc. Soc. Exp. Biol. Med. 140: 1136, 1972). have demonstrated a sex difference in the behavioral responses of rats to orally administered marijuana extract (ME). Tn order to eliminate possible sex differences in absorption of ME from the G.I. tract, ME was administered i.v. to male and female rats in a dose of delta-9-THC of 1, 2 or 4 mg/kg. Responses of females were significantly greater than responses of males at each dose. In further studies, tissue distribution of delta-9-THC was examined. ^{14}C-delta-9-THC was diluted with unlabeled ME to a final concentration of delta-9-THC of 2 mg/ml (14.4 mu-C/mg). The radiolabeled extract was administered i.v. to 6 male and 6 female rats in a dose of delta-9-THC of 2 mg/kg (28. 8 mu-C/kg). Forty-five min. after drug administration, levels of radioactivity of delta-9-THC and metabolites were significantly higher in brain, liver, muscle, and plasma of female than of male rats. The higher concentration of delta-9-THC and/or metabolites in the brain of females may account for their greater behavioral response to ME.

COLLINS, R.C., CASHAW, J.L. and DAVIS, V.E. Dopamine-derived tetrahydroisoquinoline alkaloids - - inhibitors of neuroamine metabolism. Biochemical Pharmacology 22: 2337-2348 (1973)

The formation of salsolinol and tetrahydropapaveroline (THP) in vitro as aberrant metabolites of dopamine has been established previously. Demonstrating the formation of these compound in vivo is complicated by the probability that they are extensively metabolized. The present studies indicate that a primary metabolic route for these compounds may be methylation of one or more of the free hydroxyl groups catalyzed by catechol-O-methyl transferase (COMT). Through the use of a partially purified COMT preparation from rat liver, the maximal velocities of salsolinol and THP O-methylation proved to be three to five times the maximal velocities of norepinephrine and dopamine O-methylation. The Michaelis constants determined for salsolinol, norepinephrine and dopamine are similar, whereas the K_m of COMT for THP (0.03 mM) is approximately one-tenth that of the above substrates. Salsolinol and THF are competitive inhibitors of dopamine O-methylation in vitro, their calculated inhibitor constants (Ki values) being 0. 13 and 0.02 mM respectively. The effects of these two alkaloids on rat brain monoamine oxidase (MAO) activity were also measured. They were found to be equally potent substrate competitive inhibitors of rat brain MAO in vitro, with calculated Ki values of 0.14 mM (salsolinol) and 0. 20 mM (THP). These data suggest that, if formed in vivo under certain pharmacological conditions, aberrant neuroamine-derived alkaloids may alter the metabolic disposition of endogenous neuroamines with resultant modification of adrenergic function.

CREESE, I. and SNYDER, S.H. Receptor binding and pharmacological activity of opiates in the guinea pig intestine. The Journal of Pharmacology and Experimental Therapeutics (in press)

CROMBIE, L., PONSFORD, R., SHANI. A., YAGNITINSKY. B. and MECHOULAM, R. Photochemical production of cannabicyclol from cannabichromene. Tetrahedron Letters 55: 5771-5772 (1968)

DAVIS, J.M. , JANOWSKY, D.S. and EL-YOUSEF, M.K. The biology of lithium. Lithium: Its Role in Psychiatric Research and Treatment. Edited by S. Gershon and B. Shopsin. New York: Plenum Publishing Company (in press)

DAVIS. J.M., JANOWSKY. D.S., EL-YOUSEF, M.K. and SEKERKE, H.J. Psychostimulants and the cholinergic-adrenergic balance. Advances in Neuropsychopharmacology. Praha: Avicenum Press, 1973.

DAYTON, H.E. and INTURRIS; C.E. Urinary excretion of naltrexone and its metabolites in man, rabbit, monkey and rat. Federation Proceedings 34 (1975)

For abstract, see Section I. Methodology of Drug Research.

DeCATO, L., JR., and ADLER, F.L. Neutralization of morphine activity by antibody. Research Communications in Chemical Pathology and Pharmacology 5(3): 775-788 (May, 1973)

Globulins from a hyperimmune anti-bovine serum albumincarboxymethyl-morphine (CMM-BSA) serum reduce the depressant action of morphine upon the contractions of the electrically stimulated guinea pig ileum. This activity can be shown to be a stoichiometric function of the specific anti-morphine antibody in the globulin preparation. Preliminary data indicate that idea obtained from CMM-BSA immunized guinea pigs are less reactive towards morphine than those obtained from BSA immunized controls.

DeCATO, L., JR. and ADLER, F.L. Recurrence of morphine excretion after single and multiple dose administration. Federation. Proceedings 33(3): 473 (March, 1974)

For abstract. see Section I. Methodology of Drug Research.

DENBER, H.C. Studies on mescaline: Intracellular localization. Proceedings of the 7th International Congress on Biochemistry 5: 1031 (1967)

DEWEY, W.L., HARRIS, L.S. and PATRICK, G.A. Annual report on narcotic antagonists. Committee on Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council (in press)

DEWEY, W.L., JENKINS, J., O'ROURKE, T. and HARRIS, L.S. The effects of chronic administration of trans-delta-9-tetrahydrocannabinol on behavior and the cardio-vascular system of dogs. Archives internationales de Pharmacodynamie et de Therapie 198: 118-131 (1972)

This daily intravenous administration of delta-9-tetrahydrocannabinol (delta-9-THC) produced a marked tolerance to the behavioral, effects of this compound in six mongrel dogs. Similar results were obtained with delta-8-THC in the only dog tested. The minimal effective acute i.v. dose of delta-9-THC to produce ataxia and other behavioral changes is 0.5 mg/kg. In one dog, the effects of 161 mg/kg delta-9-THC given intravenously after chronic treatment were less than those observed following 0.5 mg/kg in a drug naive dog. There were no behavioral responses which would indicate a withdrawal syndrome following abrupt stopping of the medications. Tolerance to the behavioral effects of delta-9-THC developed over a range of doses when the injections were made only once every 8 days. Behavioral tolerance could still be observed 23 days after the last injection of delta-9-THC in a tolerant dog. Initially delta-9-THC produced bradycardia in four of seven dogs tested but this changed to tachycardia at higher doses of delta-9-THC on approximately day 6 or 8 of treatment. There was no significant change in blood pressure in these dogs after either acute or chronic administration.

DEWEY, W.L., McMILLAN, D.E., HARRIS, L.S. and TURK. R.F. Distribution of radioactivity in brain of tolerant and nontolerant pigeons treated with ^{3}H-delta-9-tetrahydrocannabinol. Biochemical Pharmacology 22: 399-405 (1973)

Levels of radioactivity in the brain stem, cerebellum, temporal cortex and frontal cortex of birds tolerant to delta-9-tetrahydrocannabinol (delta-9-THC) did not differ significantly from levels in the same tissue of nontolerant birds after administration of ^{3}H-delta-9-THC. Levels of radioactivity in the lungs of both tolerant and nontolerant birds were similar to the levels of radioactivity in the brain areas after ^{3}H-delta-9-THC; however, higher levels of radioactivity were found in the livers of both groups of birds than were found in the brains. Approximately 0.1 per cent of the total dose of radioactivity was in the brain of both tolerant and nontolerant birds 2-5 hr after injection. When pigeons were injected repeatedly (seven times in 2 weeks) with ^{3}H-delta-9-THC, there was some accumulation of radioactivity in brain and lung, and an even greater accumulation in liver. These data suggest that tolerance to delta-9-THC in pigeons is not due to a decreased concentration of total cannabinoids in the brain.

DEWEY, W.L., MARTIN, B.R. and HARRIS, L.S. Chronic effects of delta-9-THC in animals: Tolerance and biochemical changes. Presented at the First International Meeting on Cannabis, 1974.

Tolerance has been shown to develop to almost every pharmacological effect of delta-9-THC in laboratory animals. The magnitude of the tolerance is large, it has a rapid onset, a long duration, and is not the result of either decreased absorption or altered metabolism. Recent experiments have demonstrated that the distribution of radioactivity is similar in tolerant and nontolerant dogs following an intravenous injection of 3H-delta-9-THC given 30 minutes prior to sacrifice. However, significantly, less radioactivity was found in the lymph nodes, pituitary, kidney cortex, and liver of the tolerant dogs. In the brain, the putamen had significantly less radioactivity following chronic medication. Also, there was significantly less radioactivity in the gray areas of the tolerant as compared to the nontolerant animals. The gray areas of the cortex and cerebellum had more radioactivity than the white matter in both groups. Subcellular fractionation of the brains was performed. Considerable quantities of radioactivity were found in the nerve ending fractions of both groups. The synaptic vesicle subfraction of the tolerant dogs contained significantly less radioactivity than the subfraction from nontolerant animals. Solvent extraction followed by thin layer chromatography revealed that 45% of the total radioactivity in the brain of both groups was due to the parent compound, delta-9-THC; less than 15% was due to the 11-OH metabolite. These results suggest that an alteration in metabolism is not responsible for the tolerance to delta-9-THC in the dog. Experiments in other species are in progress to elucidate the importance of the role of the reduced levels of radioactivity in synaptic vesicles in the mechanism of tolerance.

DEWEY, W.L., MARTIN, B.R., HARRIS, L.S. and BECKNER, J.S. Disposition of H^3-delta-9-tetrahydrocannabinol in brain of pregnant dogs and their fetuses. The Pharmacologist 16(2): 397 (1974)

Delta-9-tetrahydrocannabinol (THC) has been shown qualitatively to cross the placental barrier and enter fetal brain. To quantitate the amount of THC that accumulates in the fetal brain and to determine its subcellular distribution, two pregnant dogs were given 0.5 mg/kg of H^3-THC and sacrificed at the time of peak behavioral effect (30 min.). The brains from the mothers and the fully-developed fetuses (n-15) were removed, homogenized in isotonic sucrose and subfractionated by centrifugation. The concentration of THC plus metabolities (x + SE) in homogenates of mother and fetal brains was 340 + 27 ng/g and 85 ± 4 ng/g brain, respectively. The radioactivity in the brain of mothers was located primarily in the crude mitochondrial fraction (45%). while the rest was distributed among the crude nuclear (24%). microsomes (11%) and supernatant fractions (15%). The distribution of radioactivity in the fetal brains differed markedly from that in the maternal brains. In the fetal brains, the crude mitochondria contained only 19%, whereas the microsomes and the supernatant contained 22 and 32%. respectively. A positive correlation was found between the distribution of radioactivity and phospholipid content in fetal and maternal brains.

DEWEY, W.L. and TURK, R.F. The excretion and metabolism of ^{3}H-delta-9-THC in intact and bile duct cannulated rats. Federation Proceedings 31(2):506 (March-April, 1972)

The excretion and metabolism of 3H-delta-9-tetrahydrocannabinol (THC) which was administered orally (p.o.) and intravenously (i.v.) in intact and bile duct cannulated rats were investigated. Approximately 60 to 70 percent of the total radioactivity given was excreted during 96 hours after the administration to each group of rats. The excretion of radioactivity was minimal in each group beyond 48 hours after drug administration. The major route of excretion following the i.v. route in bile cannulated rats was by way of bile (59 percent; feces: 3 percent), whereas more radioactivity was excreted in feces (42 percent) than bile (21 percent) when the drug was given p.o. The majority of the radioactivity excreted in the feces of the orally medicated rats was extractable in petroleum ether (P.E.) and was shown to be delta-9-THC by thin layer chromatography (TLC). The majority of the radioactivity excreted in feces in noncannulated rats was not extractable in P.E. or diethyl ether (D.E.), but appeared in subsequent methanol and water extracts. It is confirmed by TLC that the radioactivity is associated with metabolites of delta-9-THC. Less than 1 percent of the radioactivity excreted in bile was extractable in P.E., and only 8 percent was extractable in D.E.; the rest was associated with more polar metabolites. Less than 10 percent of the radioactivity given was excreted in the urine of each group. Less than 0.1 percent of the total excreted in urine was extractable by P. E., and less than 5 percent by D. E.

DlNGELL, J.V., MILLER, K.W., HEATH. E.C. and KLAUSNER, H.A. The intracellular localization of delta-9-tetrahydrocannabinol in liver and its effect on drug metabolism in vitro. Biochemical Pharmacology 22: 949-958 (1973)

In the hepatic cell delta-9-tetrahydrocannabinol (THC) is localized in nuclei and microsomes. The intracellular binding of THC affects hepatic drug metabolism: nuclei markedly reduce the metabolism of THC by hepatic microsomes; THC inhibits the microsomal oxidation of aminopyrine and hexobarbital, the conjugation of estradiol and rho-nitrophenol and enhances the reduction of rho-nitrobenzoic acid. The metabolism of THC, in vitro, is strikingly inhibited by SKF-525A but not by desipramine, nortiptyline and iprindole which are potent inhibitors of the oxidation of other drugs.

DOMINO, E.F. Cholinergic mechanisms in narcotic dependence and withdrawal. Journal de Pharmacologic 5(Supplement 1): 42 (1974)

The role of the central cholinergic system in morphine dependence and withdrawal was studied in male Holtzman rats. Two different methods of producing dependence were used. The first involved bid injections of ascending does of morphine from 10 to 200 mg/kg l.p. for 2 and 8 weeks. The second method involved morphine base pellets 75 mg/kg s.c. for 3 days. Morphine withdrawal was precipitated either by not giving any additional doses of morphine or by nalorphine or naloxone 10 mg/kg i.p. Total brain acetylcholine (ACH) and its utilization using hemicholinium-3 (HC-3) or acetylseco hemicholinium (acetylseco-HC-3) was determined using the frog roctus bioassary or pyrolysis gas chromatography. The surprising finding was that the pellet method of producing morphine dependence and withdrawal caused no significant change in total brain ACH or its utilization. On the other hand, chronic morphine injections for weeks produced a striking decrease in total brain ACH and altered its utilization during morphine withdrawal, either 48 hr after stopping morphine or following nalorphine or naloxone administration. It is concluded that the method and duration of morphine dependence markedly affects the results obtained regarding central ACH utilization.

DOMINO, E. F. Clinical pharmacology of marijuana and its derivatives. Michigan Medical Center Journal 37: 1-6 (1967)

DOMINO, E. F. Neuropsychopharmacologic studies of marihuana: Some synthetic and natural THC derivatives in animals and man. Annals of the New York Academy of: Sciences 191: 165-191 (1971)

After serving a pharmacologic smorgasbord, what can one conclude about Cannabis and its natural or synthetic THC derivatives? Perhaps what stands out most clearly is that these agents are primary depressants of central nervous system function. However, they possess a unique spectrum of pharmacological actions with only superficial relation to various other psychoactive drugs. The chemistry an? pharmacology of marijuana are distinct from other central nervous system depressants, yet it shares some properties with ethyl alcohol, general anesthetics like nitrous oxide, and psychotomimetics like LSD-25. The recent report to the Congress on "Marijuana and Health" emphasizes this as well. Dosage level is all-important! In low doses these drugs produce an intoxication that in some ways resembles that of ethyl alcohol or low concentrations of nitrous oxide. There are, however, definite subjective differences. In Table 4 are summarized some of the comparative aspects of delta-9-THC, ethyl alcohol, morphine LSD-25, nitrous oxide and scopolamine and phencyclidine on various pharmacological parameters. From a scientific point of view, there is great danger in presenting any such table because the question of dose and species is always a critical factor. If the reader accepts such limitations, it is obvious that delta-9-THC has its own peculiar spectrum of pharmacology. Whether it has therapeutic merit is impossible to answer affirmatively as yet. We do have available a large variety of sedatives, analgesics, etc. Only further research will tell whether delta-9-THC and related compounds will remain of primary social, rather than medical, consequence.

DOMINO, E.F., HUDSON, R.D. and ZOGRAFI, G. Drugs Affecting the Central Nervous System, Vol. 2. Edited by A. Burger. New York: Marcel Dekker, Inc., 1968. Pp. 327-397.

DOMINO, E.F. and WILSON, A.E. Decreased rat brain acetylcholine utilization following heroin and cross tolerance to l-methadone. Biochemical Pharmacology (in press)

DOMINO, E.F. and WILSON, A.E. Failure to find a decrease in brain acetylcholine in morphine pellet implanted rats given naloxone. Psychopharmacologia (in press)

DREW, W.G, and MILLER, L.L. Cannabis: Neural mechanisms and behavior--a theoretical review. Pharmacology 11: 12-32 (1974)

The hypothesis is advanced that marihuana and especially delta-9-tetrahydrocannabinol, impair certain aspects of hippocampal neural functioning which are necessary for normal cognitive operations. It is suggested that many of the cognitive alterations induced by cannabinoids may be attributable to interference with cholinergic mechanisms. Both pharmacological and behavioral evidence are cited to support this hypothesis.

DUARTE-ESCALANTE, O. and ELLINWOOD, E.H., JR. Central nervous system cytopathological changes in cats with chronic methadrine intoxication. Brain Research 21: 151-155 (1970)

DUARTE-ESCALANTE, O. and ELLINWOOD, E., JR. Depletion of biogenic amines and enhancement of cholinargic activity in the olfactory bulb and central olfactory connections with chronic methedrine intoxication. Arquivos de Neuro-Psiquiatria 28(2): 110-117 (June, 1970)

Macrosmatic animals under the influence of chronic doses of amphetamine develop stereotyped patterns of sniffing, looking, gnawing and grooming. The most prominent stereotopy in cast is repetitive sniffing. The purpose of this report is to present evidence of histochemical changes in the olfactory system of cats, which had developed a marked sniffing stereotopy with prolonged methedrine treatment.

DUARTE-ESCALANTE. O. and ELLINWOOD, E.H., JR. Effects of chronic amphetamine intoxication on adrenegic and cholinergic structures in the central nervous system: Histochemical observations in cats and monkeys. Current Concepts in Amphetamine Abuse. Edited by E.H. Ellinwood, Jr. and S. Cohen. Washington, D.C.: U.S. Government Printing Office, 1972. Pp. 97-106.

Histochemical methods were used to study material from the central nervous systems of 25 cats and four rhesus monkeys acutely or chronically intoxicated with methamphetamine. Material from the animals acutely intoxicated showed a decrease of monoamine fluorescence in the nerve terminals but no changes in cholinergic activity. The material from chronically intoxicated animals showed: 1) a complete disappearance of monoamine fluorescence from the nerve terminals and from most of the reticular neurons in the brainstem; 2) an increase of serotonin fluorescence in the small neurons of the middle structures of the brain stem and olfactory bulb; 3) an increase of cholinergic activity in reticular areas of the brainstem, cerebellum, and olfactory system; and 4) structural changes in some reticular neurons from the medulla oblongata and the pons. From our observations, those changes appear to be related to a direct and repetitive effect of amphetamine on the enzymatic systems of both adrenergic and cholinergic mechanisms at the cellular level.

EDERY, H., GRUNFELD, Y., BEN-ZVI, Z. and MECHOULAM, R. Structural requirements for cannabinoid activity. Annals of the New York Academy of Sciences 191:40 (1971)

EIDELBERG, E. and SCHWARTZ, A.S. Consequences of selective brain biogenic depletion upon the effects of morphine in rats. Committee on Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council. 1970. Pp. 6422-6427.

ESTEVEZ. V.S., ENGLERT, L.F. and HO, B.T. Effect of SKF-525-A on the metabolism of (-)-delta-9-tetrahydrocannabinol in the rat brain and liver. Research Communications in Chemical Pathology and Pharmacology 8(2): 389-392 (June, 1974)

Treatment of rats with SKF-525-A prior to receiving tritium labeled (-)-delta-9-tetrahydrocannabinol (delta-9-THC) resulted in nearly 50% decrease of 11-OH-delta-9-THC in both the brain and liver as compared with the animals without SKF-525-A pretreatment. The microsomal oxidation inhibitor also caused a reduction of the dihydroxylated metabolite, 8,11-$(OH)_2$-delta-9-THC, to 14% of control values. The large reduction of the acid metabolite in the brain (65% of control) and the liver (16% of control) by SKF-525-A indicates the oxidative pathway producing the acid is a microsomal process.

ESTEVEZ, V.S., ENGLERT, L.F. and HO, B.T. A new methylated metabolite of (-)-11-hydroxy-delta-8-tetrahydrocannabinol in rats. Research Communications in Chemical Pathology and Pharmacology 6(3): 821-827 (November, 1973)

A new metabolite of (-)-11-hydroxy-delta-8-tetrahydrocannabinol (11-HO-delta-8-THC) was identified in the rat brain and liver as 1-Q-methyl-11-HO-delta-8-THC. Pretreatment of animals with SKF-525A resulted in an increased amount of this methylated metabolite, and a concomitant decrease of two other metabolites, the dihydroxylated delta-8-THC and an acidic compound.

FANN, W.E., DAVIS, J.M., JANOWSKY, D.S., CAVANAUGH, J.H., KAUFMANN, J.S., GRIFFITH, J.D. and OATES, J.A. Effects of lithium on adrenergic function in man. Clinical Pharmacology and Therapeutics 13(1): 71-77 (1972)

Lithium is an effective agent in the treatment of mania. Since an abnormality of biogenic amines has been postulated to be a causative factor in mania and depression and since lithium has been found to alter biogenic amines in many animal systems, the effects of lithium on adrenergic function in man was investigated. The blood pressure response to infused norepinephrine (NE) and tyramine was investigated in 8 hypomanic patients who were studied during a control period and after 7 to 10 days of lithium treatment. Lithium decreased the pressor effect produced by NE by 22 + 0.6 per cent. Lithium failed to alter the pressor effect to infused tyramine. Lithium failed to alter platelet serotonin content. Lithium decreased the pressor response to infused NE in man.

FARROW, J.T. and VANVUNAKIS. H. D-lysergic acid: Binding to subcellular fractions from rat brain. Nature 237: 164 (1972)

FENIMORE, D.C., FREEMAN. R.R. and LOY, P.R. Determination of delta-9-tetrahydrocannabinol in blood by electron capture gas chromatography. Analytical Chemistry 45(14): 2331-2335 (December, 1973)

For abstract, see Section I. Methodology of Drug Research.

FETTERMAN, P.S., KEITH, E.S., WALLER, C.W., GUERRERO, O., DOORENBOS. N.J. and QUIMBY, M. W. Mississippi-grown Cannabis sativa L: Preliminary observation on chemical definition of phenotype and variations in tetrahydrocannabinol content versus age, sex and plant part. Journal of Pharmaceutical Sciences 60(8): 1246-1249 (August, 1971)

Nine strains of Cannabis sativa L. (marijuana) were grown for research by the University of Mississippi. The seeds for these strains were obtained from Iowa, Minnesota, Mexico, Turkey, Italy, France. and Sweden. The cannabinoid content was determined using GLC, and the material was divided into two chemical phenotypes according to cannabinoid content. These phenotype categories are used to differentiate between drug-type and fiber-type Cannabis sativa. In addition, the (-)-delta-9-trans-tetrahydrocannabinol content was determined for both male and female plants, various plant parts, and a Turkish variety during various stages in its growth.

FETTERMAN, P.S. and TURNER, C.E. Constituents of Cannabis sativa L. I: Propyl homologs of cannabinoids from an Indian variant. Journal of Pharmaceutical Sciences 61(9): 1476-1477 (September, 1972)

Cannabidivarin and tetrahydrocannabivarin are shown to be present in an Indian variant of Cannabis sativa L. (marijuana) in Mississippi. GC and mass spectrometry were used for identification. Indications are that these compounds are present as acids in fresh material.

FINK, M. Brain, behavior and anticholinergic drugs. Anticholinergic Drugs, and Brain Functions in Animals and Man. Edited by P. Bradley and M. Fink. Amsterdam, the Netherlands: Elsevier, 1967. Pp. xii-xvi.

FINK, M. Drugs, EEG and behavior. Chapter X of Drugs and the Brain. Edited by P. Black. Baltimore, Maryland: Johns Hopkins Press, 1969. Pp. 149-160.

FINK, M. and ITIL, T. EEG and behavioral aspects of the interaction of anticholinergic hallucinogens with centrally active compounds. Anticholinergic Drugs and Brain Functions in Animals and Man. Edited by P. Bradley and M. Fink. Amsterdam, the Netherlands: Elsevier, 1967. Pp. 149-168.

FINK, M., SIMEON, J. and SPERO, M. Clinical and EEG studies of doxepin: An interim report. Psychosomatics 10: 14-17 (1969)

FISHMAN, J., COTTER. M.L. and NORTON, B.I. Narcotic antagonists. 2. Preparation and biological stability of naxolone-7, 8-^{3}H. Journal of Medicinal Chemistry 16: 556-557 (1973)

FISHMAN, J., NORTON, B., COTTER, M.L. and HAHN, E.F. Preparation of morphine-6-^{3}H and its isotopic stability in man and in rat. Journal of Medicinal Chemistry 17(7): 778-781 (1974)

FISHMAN, J., NORTON, B. and HAHN, E. Differential distribution of opiate agonists and antagonists in the rat brain as determined by double isotope techniques. Presented at the meeting of the American Society of Biological Chemists, 1974.

For abstract, see Section I. Methodology of Drug Research.

FISHMAN, J., ROFFWARG, H. and HELLMAN, L. Disposition of naloxone-7, 8-^{3}H in normal and narcotic-dependent men. The Journal of Pharmacology and Experimental Therapeutics 187(3): 575-580 (1973)

For abstract, see Section I. Methodology of Drug Research.

FOLTZ, R.L., FENTIMAN, A.F, JR., LEIGHTY. E.G., WALTER, J.L., DREWES, H.R., SCHWARTZ, W.E., PAGE, T.F., JR. and TRUITT. E.G., JR. Metabolite of (-)-trans-delta-8-tetrahydrocannabinol: Identification and synthesis. Science 168: 844-845 (May, 1970)

The major metabolite of (-)-trans-delta-8-tetrahydrocannabinol observed in vivo and formed by hepatic microsomes in vitro is 11-hydroxy-trans-delta-8-tetrahydrocannabinol. The metabolite was identified spectroscopically and was synthesized from trans-delta-8-tetrahydrocannabinol. In tests with rats, the metabolite produced behavioral effects similar to those imparted by delta-8- and delta-9-tetrahydrocannabinol.

FOOTE, R.S. and JONES, L.A. An analysis of the phytosterols of two varieties of Cannabis. Agricultural and Food Chemistry 22(3): 534-535 (May-June, 1974)

The quantitative determination of the 3-beta-hydroxysterols in American-grown (MS-13) and Thailand-grown Cannabis has been accomplished. The Thailand sample showed no free sterols although it contained the highest total sterol content. No campesterol was found as the glycoside in the MS-13 and Thailand sample while the Thailand sample contained no stigmasterol as the glycoside.

FORBES, J.E., DEWEY, W.L. and HARRIS, L.S. The effect of narcotics and narcotic antagonists on ganglionic transmission in rat. Federation Proceedings (in press)

Postganglionic potentials were evoked in the superior cervical ganglia by supramaximal biphasic stimuli applied to the sympathetic trunk at a frequency of 1/sec. The evoked postganglionic potentials were recorded from the external carotid nerve and displayed on a Tektronix oscilloscope after being amplified by a Grass P5-11 preamplifier. Permanent records were made by photographing the evoked potentials with a Grass Kymograph camera. The drugs were administered through a 27 gauge needle inserted into the common carotid artery. Of the pure narcotics studied, morphine (2. 5 mg/kg), meperidine (1 mg/kg), and methadone (1 mg/kg), produced inhibition of the evoked postganglionic potentials, Levorphanol (2.5 mg/kg) had no effect. Pentazocine (1.5 mg/kg) produced inhibition of the evoked postganglionic potentials while cyclazocine (0.5 mg/kg) and nalorphine (2.5 mg/kg) were inactive. Naltrexone (1.25 mg/kg) was found to produce inhibition of the evoked postganglionic potentials while naloxone (2.5 mg/kg) had no effect. The evoked postganglionic potential induced by the narcotics inhibitions were not antagonized by naloxone. Because of the lack of tolerance development to the inhibition or antagonism by naloxone, it was concluded that the inhibition of the evoked postganglionic potentials was non-specific.

FORREST, F.M., FORREST, I.S. and SERRA, M.T. Modification of chlorpromazine metabolism by some other drugs frequently administered to psychiatric patients. Biological Psychiatry 2: 53-58 (1970

Phenobarbital Sodium and Aludrox, as representative of sedatives or antacids frequently prescribed for patients on chronic phenothiazine therapy, were studied with regard to their effect on urinary chlorpromazine excretion. Phenobarbital as an inducer of additional drug metabolizing enzymes in hepatic microsomes, was found to increase the rate of urinary chlorpromazine excretion by 10-81%. Conversely, epileptic patients normally receiving maintenance barbiturates in addition to chlorpromazine, showed 17-55% decreases in urinary chlorpromazine excretion when their barbiturates were withdrawn for 7 days. Hence, phenobarbital sodium may be of interest in cases of acute chlorpromazine toxicity. Aludrox, acting as a physical absorbent of simultaneously administered chlorpromazine, decreased the urinary chlor excretion rate by 10-45% thus lowering chlor. efficiency. However, these decreases could be reduced when the two medications were spaced at 2 hr. intervals.

FORREST, I.S., BOLT, A.G. and ABER, R.C. Metabolic pathways for the detoxication of chlorpromazine in various mammalian species. Agressologie 9(2): 259-265 (1968)

FORREST, I.S. and BROOKES, L.G. In vivo and in vitro 3H-chlorpromazine in various mammalian species. Proceedings of the 7th Congress of Collegium Internationale Neuro-Psychopharmacologicum, Prague, Czechoslovakia, August, 1970.

FORREST, I.S., BROOKES, L.G., DENEAU, G.A. and MELLET, L.B. In vivo and in vitro metabolism of ^{3}H-chlorpromazine in the rhesus monkey. The Pharmacologist 12: 273 (1970)

Urinary and fecal excretion of chlorpromazine and its metabolites was studied in 8 adult rhesus monkeys chronically dosed with 30 mg/kg per day for several years. Approximately 20% of the administered dose was found to be excreted via the urine, while fecal excretion accounted for less than 5%. The urinary metabolites present were similar to those seen in man, but an unknown conjugate, probably derived from 8-hydroxy-chlorpromazine constituted nearly 10% of the urinary and fecal drug fractions. Some of the animals also received tracer doses of chlorpromazine, tritium labeled at position 9 of the nucleus. These served in the estimation of the biological half-life of chlorpromazine and in the quantification of drug metabolites isolated by thin layer chromatography. In vitro metabolism of 3-H-chlorpromazine was also determined using hepatic inicrosomes of untreated rhesus and squirrel monkeys. Both species of primates showed similarities to man, but differences between them were significant.

FORREST, I.S., FOX, J., GREEN, D.E., MELIKIAN, A.P. and SERRA, M.T. Total excretion of ^{3}H-chlorpromazine and ^{3}H-prochloperazine in chronically dosed animals: Balance sheet. The Phenothiazines and Structurally Related Drugs. Edited by I.S. Forrest, C.J. Carr and E. Usdin. New York: Raven Press, 1974.

Phenothiazine drugs are administered to large numbers of patients, frequently for indefinite periods of time and in high daily doses. It therefore seems important to study their biotransformation, distribution, and excretion in man and appropriate animal models as parameters which eventually will help elucidate their mode of action. After 20 years of intensive study of the phenothiazines. even as simple an aspect as a balance sheet--input versus output under chronic or acute conditions of drug administration--is a controversial subject. Using three species of mammals and two phenothiazine drugs tritiated at the metabolically insensitive position 9 of the nucleus, it was found that under chronic drug dosage, recovery of the label was essentially complete within 10 to 20 days. Lesser recoveries prevailed under acute conditions. Correlated chemical assays (spectrophotometric or chromatographic) proved less satisfactory and from 10 to 30% of the daily dose excreted in urine and feces according to radioquantitation remained unaccounted for. This discrepancy is tentatively attributed to inadequate methodology for determination of all known and unknown metabolites of the phenothiazine drugs.

FORREST, I.S. and GREEN, D.E. Phenothiazines: Metabolism and analytical detection. Journal of Forensic Sciences 17: 592-617 (1972)

FORREST, I.S., GREEN, D.E., OTIS, L.S. and WÜRSCH. M.S. Excretion of ^{3}H-delta-9-tetrahydrocannabinol (THC) in rhesus and squirrel monkeys. Federation Proceedings 31: 506 (1972)

^{3}H-delta-9-THC was orally administered to Rhesus and Squirrel monkeys who had previously received 1 mg/kg unlabeled delta-9-THC for 4 days. Urinary and fecal excretion of the label was followed for 2 weeks and sporadically thereafter. In Rhesus, 22% to 26% of the label was excreted in the urine within 14 days, while corresponding fecal excretion amounted to 40% to 52%. Fecal excretion of minor quantities continued for several weeks thereafter, and Rhesus appeared a suitable model animal for comparison with man. Delta-9-THC metabolism in Squirrel monkey, however, did not appear comparable to that of man. Within 14 days only 1% to 5% of the label was eliminated with the urine, while between 53% and 60% appeared in the first day's feces of the animals, indicating very poor absorption of delta-9-THC. From 88% to 91% of the label was found in the urines and feces of this species within 2 weeks, while only subsequently detected in the fur of both species, reaching peak excretion by this route approximately 3 months after ingestion of ^{3}H-delta-9-THC.

FORREST, I.S., GREEN, D.E., ROSE, S.D., SKINNER, G.C. and TORRES, D.M. Fluorescent-labeled cannabinoids. Research Communications in Chemical Pathology and Pharmacology 2(6): 787-792 (November, 1971)

Nine different cannabinoids were converted to their 1-dimetliylamino-naphthalene-5-sulfonates. Mixtures of the fluorescent-labeled cannabinoids were separated by thin layer chromatography. and individual spots were detectable at the 0.5 nanogram level. This sensitivity appears adequate to develop an assay for biotransformation products of cannabinoids in human urine after the smoking of a single cigarette.

FORREST, I.S., GREEN, D.E. and SERRA, M.T. An attempt to bridge some gaps in the knowledge of chlorpromazine metabolism and excretion. Proceedings of the Western Pharmacological Society (in press)

FORREST, I.S., GREEN, D.E. and SERRA, M.T. The use of XAD-2 nonionic polymeric adsorbent in the analysis of chlorpromazine and its metabolites. Psychopharmacology Bulletin 9(2): 20-21 (1973)

FORREST, I.S., GREEN, D.E. and WÜRSCH, M.S. ^{3}H-delta-9-tetrahydrocannabinol (THC) metabolites in rhesus monkey urine: Efficient new extraction procedures and implications for metabolite structures. Abstracts of Volunteer Papers. Fifth International Congress on Pharmacology. San Francisco, California, July, 1972. Pp. 71.

FORREST, I.S., KOSEK, J.C., ABER, R.C. and SERRA. M.T. Rabbit as a model for chlorpromazine-induced hyperpigmentation of the skin. Biochemical Pharmacology 19:849-852 (1970)

Hyperpigmentation of exposed skin areas, comparable to that seen in less than 1 per cent of patients chronically dosed with chlorpromazine after intensive long-term therapy, has been produced in sixteen out of sixteen chronically dosed pigmented rabbits, receiving between 20-30 mg/kg per day. Thirty-min u.v. irradiation of a clipped or shaved area produced clear-cut hyperpigmentation of naturally pigmented skin areas in about 4 weeks. The characteristic occurrence of granular pigment in the dermis which is normally free of pigment was also observed. Hyperpigmented rabbits did not develop any concomitant ocular pathology, as seen in some patients on long-term, high-dosage chlorpromazine therapy.

FORRES, I.S., OTIS, L.S., ERRA, M.T. and SKINNER, G.L. Passages of ^{3}H-chlorpromazine and ^{3}H-delta-THC into the hair (fur) of various mammals. Proceedings of the Western Pharmacological Society 15: 83 (1972)

A number of tests were carried out in different species of mammals receiving tracer doses of chlorpromazine, tritiated at the metabolically insensitive position 9 of the nucleus. Additional studies were carried out with delta-9-THC tritiated at positions 2,4,8 and 9 of the nucleus. In this instance we have no knowledge of the stability of the label nor of the various metabolites excreted with the urine and feces of primates.

FORREST, I.S., WECHSLER. M.B., BOLT, A.G. and ABER, R.C. Studies on chlorpromazine metabolites in mammalian tissues. Federation Proceedings 26(2): 353 (1967)

Available procedures have provided partial information on types and amounts of chlorpromazine metabolites selectively stored in body tissues. The present method permits estimation of the three groups of drug metabolites, i.e, 1) the largest group, unhydroxylated basic metabolites; 2) the slightly smaller group, hydroxylated metabolites of group 1); 3) the glucurosides of group 2). Groups 1) and 2) were selectively extracted from tissue specimens, and assayed spectroscopically after conversion to their respective radical ions. Group 3) was measured as group 2) after enzymatic hydrolysis. TLC revealed the following metabolites: Chemically unchanged chlorpromazine, its nor_1-derivative and traces of chlorpromazine sulfoxide; 7-hydroxychlorpromazine, its nor_1-and nor_2-derivatives and traces of their respective glucuronides. Concentrations of these groups of metabolites in autopsied human tissues are discussed with respect to dosage in patients. with and without manifestations of late side-effects of drug therapy. It was concluded that the presence of unconjugated 7-hydroxychlorpromazine in the tissues of man and experimental animals is a concomitant of normal drug metabolism, and not a toxic manifestation per se.

FRIEDNOFF, A.J. Biosynthesis of DMPEA and its metabolites in mammalian tissues. Biological Psychiatry 6(2): 412 (1973)

FRIEDHOFF, A.J. and SCHWEITZER, J. W. Amphetamine metabolism in amphetamine psychosis. Advances in Neuropsychopharmacolopy. Edited by O. Vinar, Z. Votava and P.B. Bradley. Amsterdam, the Netherlands: North Holland Publishing Company, 1972. Pp. 267-277.

Although incomplete evidence is available, the kinds of symptons appearing during amphetamine psychosis vary with the body burden of amphetamine, ranging from symptoms of increased arousal at the lowest level to those of toxic delirium at the highest. The pharmacological action of amphetamine appears to be mediated at least in part, through an interaction with catecholamines. A more profound effect on catecholamines, particularly dopamine, may be involved in the pathogenesis of amphetamine psychosis. Alternatively, a psychotomimetic metabolite of amphetamine may be produced, although this is not supported by the studies undertaken.

FRIEDHOFF, A.J., SCHWEITZER, J.W. and MILLER, J. Biosynthesis of mescaline and N-acetylmescaline by mammalian liver. Nature 237: 454-455 (June, 1972)

FRIEDHOFF, A.J., SCHWEITZER, J.W. and MILLER, J. The enzymatic formation of 3, 4-di-o-methylated dopamine metabolites by mammalian tissues. Research Communications in Chemical Pathology and Pharmacology 3(2): 293-311 (March. 1972)

In a series of experiments it was demonstrated that a dopamine metabolite, N-acetyl-3-hydroxy-4-methoxyphenethylamine (i-NAMT), can be transformed enzymatically to N-acetyl-3,4-dimethoxyphenethylamine (NADMPEA) by mammalian tissues. It can be concluded, therefore, that a 3,4-dimethoxy derivative of a catechol structure is a possible product of catecholamine metabolism.

FRIEDHOFF, A.J., SCHWEITZER, J.W. and MILLER, J. The formation of a dimethoxy derivative of dopamine in mammalian brain and liver, Proceedings of Symposium on Mechanisms of Regulation of Biogenic Amines, Lodz, Poland, 1972.

GALLAGER. D.W., SANDERS-BUSH, E. and SULSER, F. Dissociation between behavioral effects and changes in metabolism of cerebral serotonin following delta-9-tetrahydrocannabinol. Psychopharmacologia 26: 337-345 (1972)

Behavioral changes, reaction times in analgesic tests and effects on abolism of cerebral serotonin (5 HT) were monitored in male Sprague-Dawley following the administration of delta-9-tetrahydrocannabinol (THC) as a propylene of serum complex. THC (5.5 mg/kg i.p. and 1.0 mg/kg i.v.) produced charactic and reproducible behavioral effects, including catalepsy and squealing, as well as significant increases in the reaction time as determined in both the hot plate and tail flick tests for analgesis. Intraventricular injection of THC caused many of the changes seen after systemic administration of the drug. The levels of 5 ITT and the principle metabolite, 5-hydroxyindoleacetic acid (5HIAA) were measured in the brain and brainstem following THC. No significant change in the level of either was observed. Moreover, THC did not alter the turnover of cerebral 5 HT as determined by the probenecid method and did not change the increase in 5 HT following the administration of pargyline.

GAONI, Y. and MECHOULAM, R. Hashish XIV. The iso-tetrahydrocannabinols. Israeli Journal of Chemistry 6:679 (1968)

Synthetic routes we described which lead to ISO-THC's, a new series of structural isomers of the natural delta-THC. In this group of compounds a dihyrobenzopyran ring system is formed by cyclizatron of one of the phenolic groups of a cannabinoid with the C_1 carbon in the terpene moiety of the molecule.

GAONI, Y. and MECHOULAM, R. The isolation and structure of delta-1-tetrahydrocannabinol and other neutral cannabinoids from hashish. Journal of the American Chemical Society 93: 217-223 (1971)

The isolation and elucidation of the structures of delta-1-tetrahydrocannabinol (delta-1-THC), cannabigerol. cannabichromene, and cannabicyclol are described. A facile conversion of cannabidiol into delta-1-THC takes place on treatment with boron trifluoride etherate. The absolute configuration of the chiral centers at C-3 and C-4 of delta-1-THC is established as R.

GARRETT, E.R., BRES, J., SCHNELLE, K. and ROLF, L.L., JR. Pharmacokinetics of saturably metabolized amobarbital. Journal of Pharmacokinetics and Biopharmaceutics 2(1): 43-103 (1974)

For abstract, see Section I. Methodology of Drug Research.

GARRETT, E.R. and HUNT, C.A. Physicochemical properties, solubility and protein binding of delta-9-tetrahydrocannabinol. Journal of Pharmaceutical Sciences 63(7): 1056-1064 (July, 1974)

For abstract, see Section I. Methodology of Drug Research.

GARRETT, E.R. and HUNT, C.A. Picogram analysis of tetrahydrocannabinol and application to biological fluids. Journal of Pharmaceutical Sciences 62(7): 1211-1214 (July, 1973)

GARRETT, E.R. and TSAU, J. Stability of tetrahydrocannabinols I. Journal of Pharmaceutical Sciences 63(10): 1563-1574 (October, 1974)

For abstract, see Section I. Methodology of Drug Research.

GAZTANGA, P., ABRAMS. R., SIMEON, J., JONES, T. and FINK, M. Clinical evaluation of GP-41299: An antianxiety agent of the doxepin type. Arzneimittel-Forschung 22: 1903-1905 (1972)

GERBER, N., SMITH, R., OLSEN, G.D., LEGER, R.M. and LYNN, R.K. Investigation of methadone (M) metabolism by gas chromatography (GC) and mass spectrometry (MS). Proceedings of the Sixth International Congress of Pharmacology, Helsinki, Finland, July 20-25, 1975.

A specific gas chromatographic assay has been developed for the quantification of M and its primary metabolite. 2-ethylidene-1, 5-dimethyl-3.3-diphenylpyrrolidine (P). This involves extraction of M and P from samples (plasma. blood. urine, homogenates) at pH 9.8. reextraction of an aliquot of solvent with 0.1 N HCL, alkinization of the latter with NH_40H and final extraction into chloroform. The partition coefficient of M between 1-chlorobutane and pH 9.8 buffer is greater than 70. When Swiss-Webster mice weighing between 25-35 gm were given 530 mg of racemic M ip, approximately 50% of the drug was metabolized in about 30 min. Pre-treatment of mice with sodium phenobarbital (100 mg/kg ip daily for 4 days) caused a twofold increase in the rate of metabolism of M. Moreover, mice given one or the other isomer of M eliminated the d-isomer more rapidly than the l-, and a much larger fraction of the d-isomer was found unchanged in the urine at 200 min. In the isolated perfused rat liver there was an initial rapid decline of M in the perfusate followed by a slower decline ($^t1/2$=114 min) after 30 min. When either isomer of M or the racemic mixture was used the concentration of P increased in the mouse and in the perfusate of the isolated liver. GC-MS of methylated (CH_31, $DMSO^1$) glucuronic acid conjugates from bile gave molecular ions at m/e 525, 555, 511, 541, indicating the presence of mono- and di-hydroxylated glucuronides of P and the pyrroline metabolite.

GESSNER, P.K. Pharmacological studies of 5-methoxy-n, n-dimethyltryptamine, LSD and other hallucinogens. Psychotomimetics. Edited by D. H. Efron. New York: Raven Press, 1969. Pp. 105-118.

GESSNER, P. K. and GESSNER, T. Inhibition of ethanol acetaldyhyde disappearance in vivo by diethyldithiocarbamic acid methylester, a metabolite of disulfiriram. Presented at the Fifth International Congress on Pharmacology, Volunteer Abstracts 81 (1972)

GOLDSTEIN, A. Accurate measurement of urinary morphine. New England Journal of Medicine 286: 1417 (1972)

GOLDSTEIN, A. Biochemistry and pharmacology of the addictive process. Abstracts of the 119th Annual Meeting of the American Pharmaceutical Association, Vol. 2. Washington, D.C.: The American Pharmaceutical Association, 1972. P. 31.

GOLDSTEIN, A. and GOLDSTEIN, D.R. Enzyme expansion theory of drug tolerance and physical dependence. Chapter XIX of The Addictive States Association for Research in Nervous and Mental Disease, Vol. XLVI. Baltimore, Maryland: The Williams and Wilkins Company, 1968. Pp. 265-267.

GOLDSTEIN, A. and JUDSON, B.A. Alcohol dependence and opiate dependence: Lack of relationship in mice. Science 172: 290-292 (April 1, 1971)

According to a recently proposed hypothesis, physical dependence upon alcohol is due to the formation of an endogenous opiate. We tested the hypothesis by determining whether or not ethanol-dependent mice would show typical opiate-dependent behavior (withdrawal jumping syndrome) when challenged with the opiate antagonist naloxone. Our results do not support the hypothesis.

GORODETZKY, C.W. Abuse liability of etdrphine (M99). II. Detectability in the urine by common screening methods after subcutaneous administration in man. Federation Proceedings 33(3): 487 (March, 1974)

A single dose of 100 mu-g of M99 was administered subcutaneously to 7. subjects and all urine samples were collected for 1 day prior to and 3 days following drug administration. Each sample was analyzed for the presence of opiates by the Abuscreen^{R} radioimmunoassay (RLA) and the EMIT^{R} homogenous enzyme immunoassay, with cutoffs for "positives" of 40 and 500 ng/ml urinary morphine standards respectively. Samples were analyzed for M99 by TLC with iodoplatinate after XAD-2 resin extraction (sensitivity = 0.2 mu-g M99/ml of urine). Under blind conditions all samples were analyzed unhydrolysed and the last pre-drug and first 2 post-drug samples after both acid and glucuronidase hydrolysis. No samples gave a "positive" opiate result in either immunoassay and no M99 was detected in the TLC analyses in any urine sample. It is estimated that if as little as 14% of the administered dose had been excreted as free M99 in the first 2 hours or as little as 20% in the first 3 to 5 hours, M99 would have been detected in the TLC analyses. M99 is probably extensively metabolized and/or excreted by routes other than the urine. It is concluded that a highly euphorogenic dose of M99 is unlikely to be detected in urine samples subjected to the routine screening procedures of RIA, EMIT and TLC preceded by XAD-2 resin extraction. Thus, it is unlikely that the abuse of M99 could be diagnosed by commonly used urine screening methods.

GORODETZKY, C.W. Efficiency and sensitivity of two common screening methods of detecting morphine in urine. Clinical Chemistry 19(7): 753-755 (1973)

For abstract, see Section I. Methodology of Drug Research.

GORODETZKY, C.W. Time course of morphine (M) detection in human urine after IV morphine. Federation Proceedings 32(3): 764 (March, 1973)

Two single doses of M, 6 and 12 mg/70 kg were administered IV at weekly intervals in random order to 10 subjects and all urine was collected for 1 week and pooled into 4 to 8-hr. samples. Each sample was analyzed under blind conditions by the following methods: 1. extraction unhydrolysed by organic solvent (OS) and ion exchange resin impregnated paper (IE) and after acid hydrolysis (OSH, IEH) with detection by TLC after spraying with iodoplatinate; 2 FRAT; 3 Technicon Autoanalyzer (TECH): 4 radioimmunoassay (RIA). False positives on pre-drug control urines were 0% for OS, IE, IEH and RIA, 1.3% for OSH, 9% for FRAT, and 3% for TECH. Results are shown below for % of urines positive for M for 96 hrs. after drug.

GORODETZKY, C.W., ANGEL, C.R., BEACH, D.J., CATLIN, D.H. and YEH, S.Y. Validity of screening methods for drugs of abuse in biological fluids. I. Heroin. Clinical Pharmacology and Therapeutics 15(5): 461-471 (May, 1974)

For abstract. see Section I. Methodology of Drug Research.

GORODETZKY, C.W. and KULLBERG. M.P. Time course of morphine (M) detection in human urine after i.v. heroin (H) by XAD-2 resin and TLC. The Pharmacologist 16(2): 193 (Fall, 1974)

Three single doses of H, 2.5, 5 and 10 mg/kg, were administered IV at weekly intervals in random order to 8 subjects and all urine was collected for 1 week and pooled into 4 to 8 hr. samples. Each sample was analyzed under blind conditions by TLC with iodoplatinate preceded by XAD-2 resin extraction unhydrolyzed (X) and after acid hydrolysis of urine (XH) or urine-loaded resin (XRH) (Clin Chem. 20:177, 1974). Adding M to normal urine, the concentration detectable 99% of the time (95% C.L.) by X was 80(65-100) ng/ml. False positives on pre-drug control urines were 0% for X and XH and 1% for XRH.

GORODETZKY, C.W. and KULLBERG, M.P. Validity of screening methods for drugs of abuse in biological fluids. II. Heroin in plasma and saliva. Clinical Pharmacology and Therapeutics 15(6): 579-587 (June, 1974)

For abstract, see Section I. Methodology of Drug Research.

GROCE, J.W. and JONES, L.A. Carbohydrate and cyclitol content of cannabis. Agricultural and Food Chemistry 21(2): 211-214 (March-April, 1973)

The carbohydrate and cyclitol content of Cannabis sativa grown in the United States (MS-23), Thailand, and Viet Nam was determined via silylation and gas chromatographic techniques, and the methods of isolation are described. MS-13 contained the carbohydrates ribitol, fructose, alpha- and beta-D-glucose, and sucrose and the cyclitols (+)- quebrachitol, D(-)-bornesitol, and myo-inositol. Only the Thailand sample contained (+)-inositol, whereas only the Viet Nam sample contained erythritol. The carbohydrate-cyclitol content was MS-13 greater than Thailand greater than Viet Nam.

GROSS, S.J., SOARES, JR., WONG, S.L.R. and SCHUSTER, R.E. Marihuana metabolites measured by a radioimmune technique. Nature (in press)

HAHN, D.L. and GOLDSTEIN, A. Amounts and turnover rates of brain proteins in morphine-tolerant mice. Journal of Neurochemistry 18: 1887-1893 (1971)

Mice were injected intracerebrally with radioactive leucine 30 min before decapitation. A double-label technique was used; e.g. (^{3}H) leucine in control, untreated mice and (^{14}C) leucine in morphine-tolerant (dependent) mice. Proteins were extracted sequentially from mouse brain with aqueous buffer, Triton X-100, and sodium lauryl sulphate. Each extract was subjected to electrophoresis on discontinuous, porosity-gradient acrylamide gels. When the protein patterns from untreated, acutely morphinized mice were compared with those from morphine-tolerant (dependent) mice, we observed no differences in the amounts of protein or of radioactivity in any of the 55 discrete bands.

HARIK, S.I., MOLLENBERG, M.D. and SNYDER, S.H. Ornthine decarboxylase turnover slowed by alpha-hydrazinoornithine. Molecular Pharmacology 10:41-47 (1974)

Alpha-hydrazino-ornithine is a potent and selective inhibitor of ornithine decarboxylase (L-ornithine carbosy-lyase, EC 4.1.1.17). When added to rat hepatoma cells at the time of dilution, alpha -hydrazino-ornithine elicits a dose-related increase in ornithine, decarboxylase activity and a concomitant prolongation of the apparent half-life of the enzyme from 10 min to 28 min. as determined by the rate of decline of ornithine decarboxylase activity after inhibition of protein synthesis by cycloheximide. Similarly, systemic administration of alpha-hydrazino-ornithine to nephrectomized rats induces a dose-related enhancement of ornithine decarboxylase activity in the normal and regenerating liver, which is associated with prolongation of the apparent half-life of the enzyme. In both intact liver and hepatoma cells in culture, the decrease in the turnover rate of the enzyme can account for its increased activity.

HARIK, S.I., PASTERNAK. C.W. and SNYDER, S.H. An enzymatic-isotopic microassay for putrescine. Biochimica et Biophysica Acta, 304: 753-764 (1973)

A highly sensitive enzymatic isotopic microassay procedure for the measurement of putrescine (1,4-diaminobutane) is described. The method depends on the enhancement by putrescine of the decarboxylation of S-adenosyl-L-(carboxy-^{14}C) methionine by baker's yeast (Saccharomyces cerevisiae) S-adenosyl-L-methionine decarboxylase in the presence of varying amounts of putrescine. The quantity of $^{14}CO_2$ evolved is a linear function of the amount of putrescine present. This method was used to measure the putrescine content of various tissues.

HARIK, S.I., PASTERNAK, G.W. and SNYDER, S.H. Putrescine: A sensitive assay and blockade of its synthesis by alpha-hydrazine ornithine. Polymines in Normal and Neoplastic Growth. Edited by D.H. Russell. New York: Raven Press, 1973. Pp. 307-321.

A highly sensitive and specific enzymatic-isotopic microassay procedure for the measurement of putrescine is described. The method depends on the enhancement by putrescine of the decarboxylation of ^{14}C-SAMe by baker's yeast SAMeDC. The quantity of $^{14}CO_2$ evolved is a linear function of the amount of putrescine present in the incubation mixture. The method can reliably measure 20 pmoles of putrescine, only small amounts of tissue (0.5 to 4mg) are required for the assay, and the technique is simple to perform so that 100 samples can be assayed in one working day.

This method was used to measure the putrescine content of various tissues. Data collected by this methodwere much lower than those obtained by other workers for the rat and mouse brain and liver, but our values were corroborated by an amino acid analyzer technique. Putrescine tissue levels correlated well with ODC activity and may serve as an indicator of the activity of this enzyme in tissues where ODC activity cannot be detected readily.

Alpha-HO was found to be a potent and specific in vitro inhibitor of E. coli, and rat prostate ODCs. However, when given to rats it greatly enhanced the activity of hepatic and prostatic ODC.

HARRISON, S.D., JR., CHIU, P. and MAICKEL, R.P. Polyamide thin-layer chromatographic separation of DOPA metabolites and related compounds. Journal of Chromatography 85: 151-153 (1973)

For abstract, see Section I. Methodology of Drug Research.

HENDLEY, E.D. and SNYDER, S.H. Stereoselectivity of catecholamine uptake in noradrenergic and dopaminergic peripheral organs. European Journal of Pharmacology 19: 56-66 (1972)

The stereoselectivity of noradrenaline uptake was studied in several adrenergically innervated peripheral organs of the rabbit and rat, as well as in the isolated rabbit retina. (-)- and (+)-noradrenaline bitartrate, and (-)-and (+)-amphetamine sulfate, were compared as relative antagonists of the neuronal membrane catecholamine uptake mechanism in the various organs, in order to determine stereoselectivity at both the alpha and beta carbons of noradrenaline. It was not possible to demonstrate stereoselectivity unless optimal conditions prevailed. These included the use of finely divided tissues (less than 0.5 mm on a side), of linear uptake rates, and of non-saturating levels of amines.

In the rabbit vas deferens and iris/ciliary, where noradrenaline is the predominant catecholamine and is present in high endogenous concentrations, there was a marked preference for (-)-noradrenaline and for (+)-amphetamine, in contrast with the rabbit retina where dopamine is the chief catecholamine and in which no stereoselectivity was demonstrable. These results confirmed earlier findings in the rat brain in which catecholamine uptake was stereoselective in noradrenergic brain regions but not in the corpus straitum, a dopaminergic region (Coyle and Snyder, 1969).

Cardiovascular tissues of the rabbit exhibited a reversal of the usual stercoselectivity, i.e. (+)-noradrenaline had more affinity than ( )-noradrenaline in the rabbit atrium, left ventricle and thoracic aorta, and (-)-amphetamine was more potent an inhibitor of catecholamine uptake than (+)-amphetamine in the thoracic aorta. Amphetamine stereoisomers were equipotent in the tissues of the rabbit heart. Unlike cardiovascular tissues of the rabbit, ventricular slices of the rat displayed a marked preference for ( )-noradrenaline and for (+)-amphetamine.

HENDLEY, E.D., SNYDER, S.H., FAULEY, J.J. and LaPIDUS, J.B. Stereoselectivity of catecholamine uptake by brain synaptosomes: Studies with ephedrine, methylphenidate and phenyl-2-piperidyl carbinol. The Journal of Pharmacology and Experimental Therapeutics 183(1): 103-116 (1972)

In this study we examined the stereoselectivity of catecholamine uptake into synaptosomes prepared from rat cerebral cortex or corpus striatum with isomers of ephedrine, methylphenidate and phenyl-2-piperidyl carbinol, compounds possessing two asymmetric carbons, hence, four possible stereoisomers. The four ephedrine isomers were more potent inhibitors of catecholamine uptake in the cerebral cortex than in the corpus striatum. There was a 100-fold variation in potency among the ephedrine isomers in the cerebral cortex but only a 7-fold variation in the corpus striatum. The optimal configuration at the alpha (S) and beta (R) carbons (erythro configuration) for activity of the ephedrines in both brain regions corresponds to the configurations of (+)-amphetamine and (-)-norepinephrine, respectively. In contrast. the four phenyl-2-piperidyl carbinol isomers were more potent in the corpus striatum than in the cerebral cortex, and the configuration of the most potent isomer was R at both alpha and beta carbons, i.e., threo. Also unlike the ephedrines. there was a greater variation in potency among the various phenyl-2-piperidyl carbinol isomers in the striatum than in the cerebral cortex. The methylphenidates, like phenyl-2-piperidyl carbinol, were more potent inhibitors of catecholamine uptake in the corpus striatum than in the cerebral cortex, and the threo racemate of methylphenidate was about 100 times more active than the erythro racemate in both areas. Although ephedrine, amphetamine and norepinephrine isomers show much less stereoselectivity in the corpus striatum than in the cerebral cortex, phenyl-2-piperidyl carbinol and methylphenidate isomers display more stereoselectivity in the corpus striatum than in the cerebral cortex. The relative activity among phenyl-2-piperidyl carbinol and methylphenidate isomers in inhibiting catecholamine uptake is opposite to that of ephedrine isomers.

HERNDON, B.L., BAEDER, D.H. and RINGLE. D.A. An immunoglobulin model of the morphine receptor. Federation Proceedings 33: 571 (1974)

An immunoglobulin, directed against the morphine configuration, can be produced in rabbits by subcutaneously implanting pellets made of morphine free base. If we assume this small molecule becomes immunogenic by covalent coupling to an endogenous carrier, this reaction (through the immunoglobulin it produces) could be used in binding studies as a model to interpret the nature of the morphine "receptor", perhaps a more physiologic model than one which uses pre-coupled morphine-protein complexes. Nine compounds, structurally related to morphine, were obtained. Pellets from their free bases were prepared and implanted in rabbits. After 3 courses, sera were tested for binding of ^{14}C-morphine and ^{14}C-codeine. Levorphanol and morphine produced high binding titers but with different affinities for the labeled morphine and codeine. In other tests, rabbits with antibody produced by morphine pellets were "boosted" with the morphine congener pellets and their sera studied. Compounds that produced binding sera when implanted alone also boosted morphine binding. We found no relationship between analgesic potency and a compound's ability to form an immunoglobulin that binds labeled morphine or codeine and are studying the possible relationship of immune memory to a drug's re-addiction potential.

HILL, J.H., WAINER, B.H., FITCH, F.W. and ROTHBERG, R.M. Delayed clearance of morphine from the circulation of rabbits immunized with morphine -6-hemisuccinate-bovine serum albumin. Journal of Immunology (in press)

Morphine clearance from the circulation of normal rabbits and rabbits with circulating anti-morphine antibody was studied. Individual animals were injected with a saline solution containing 99 parts unlabelled morphine and one part ^{14}C-morphine at a dose of 6 mg morphine/kg body weight. The rabbits were bled at various times after morphine injection and the amount of morphine present in the serum at each time interval was determined by liquid scintillation. Morphine could be detected in the serum of normal animals for one week following injection and up to 12 weeks following injection in at least one animal with antibodies to morphine. The rate of morphine clearance in animals immunized to morphine-6-hemisuccinate-bovine serum albumin (M-6-HS-BS A) was not significantly different from normal during the first four hours after morphine injection. However, by 24 hours after injection, the rate of morphine clearance in M-6-HS-BSA immunized animals was significantly slower than in normal animals. The amount of morphine present in the sera of the rabbits 24 hours after injection was related to the antibody concentration and independent of antibody affinity. However, the rate of morphine clearance at times greater than 24 hours was related to the relative average antibody affinity and independent of antibody concentration.

HILL, J.H, WAINER, B.H., FITCH, F.W. and ROTHBERG, R.M. The interaction of ^{14}C-morphine with sera from immunized rabbits and from patients addicted to heroin. Clinical Experimental Immunology 15: 213-224 (1973)

An intravenous injection of morphine reduced the binding of ^{14}C-morphine by sera from rabbits immunized with morphine-6-hemisuccinated bovine serum albumin. Treatment of the sera with dialysis against glycine buffer (pH3) followed by dialysis against phosphate buffered saline (PBS), conditions known to dissociate antigen-antibody complexes, restored approximately 76% of the original binding capacity. The heterogeneity of the antibody affinities was shown in both early 'nonavid' and hyperimmune 'avid' antisera by the demonstration of at least two distinct populations of antibodies. One population of antibodies formed loosely bonded antigen-antibody complexes and these complexes completely dissociated within 30 min. The second population had different dissociation times in the 'nonavid' and 'avid' antisera (15 and greater than 72 hr. respectively). The presence of the low affinity antibody resulted in different degrees of reduction of detectable binding by the standard washing procedures usually employed in the radioimmunoassay used in these studies. Washing caused less reduction in the amount of antigen bound by the more 'avid' antisera.

Seventy-three per cent of sixty-three serum samples from heroin addicts studied, contained opioid capable of inhibiting the binding of morphine in the radioimmunoassay employed. Methadone at concentrations likely to be present in sera did not interfere with the binding of ^{14}C-morphine. Sera from thirty-one of the patients were treated by dialysis against glycine buffer and PBS and then studied for the capacity to bind morphine. Only of these thirty-one sera and none of the thirty-two sera that were not pretreated bound ^{14}C-morphine suggesting that an immune response to heroin is not a significant contributing factor to opioid tolerance or the development of complications, such as pulmonary oedema, following opioid administration.

HITZEMANN, R.J. and LOH, H.H. Effect of morphine on the transport of dopamine into mouse brain slices. European Journal of Pharmacology 21: 121-129 (1973)

The effect of various concentrations of morphine on the transport of dopsmine (DA) into slices from the mouse brain cortex and diencephalon was investigated. It was observed that sub-analgetic levels of morphine, 3.5 X 10^{-8} M, produced mixed inhibition in the cortex and uncompetitive inhibition in the diencephalon. When the concentration of morphine was increased to within the therapeutic range (3. 5 X 10^{-6}), a greater effect on DA affinity rather than reaction velocity was observed in the cortex although the inhibition remained mixed. Only the increase in inhibition of DA transport observed by increasing the morphine concentration from 3. 5 X 10^{-8} to 3.5 X 10^{-6}M was blocked by the morphine antagonist naloxone. Increasing the morphine concentration in the diencephalon changed the type of inhibition from uncompetitive to mixed kinetics.

HO, B.T., ESTEVEZ, V.S. and ENGLERT, L.F. Effect of repeated administration on the metabolism of (-)-delta-9-tetrahydrocannabinols in rats. Research Communications in Chemical Pathology and Pharmacology 5(1): 215-218 (January, 1973)

Chronic administration of (-)-delta-9-tetrahydrocannabinol (delta-9-THC) to rats increases the metabolism of the compound in the liver but not in the lungs. Kidneys and brain remain inactive in metabolizing delta-9-THC.

HO, B.T., ESTEVEZ, V.S. and ENGLERT, L.F. The uptake and metabolic fate of cannabinoids in rat brains. Journal of Pharmacy and Pharmacology 25(6): 488-490 (June, 1973)

HO, B.T., ESTEVEZ, V. and FRITCHIE, G.E. The fate of 2, 5-dimethoxy-4-methylamphetamine (STP, DOM) in monkey and rat brains. Brain Research 29: 166-169 (1971)

HO, B.T., ESTEVEZ, V., ENGLERT, L.F. and McISAAC, W. M. Delta-9-tetrahydrocannabinol and its metabolites in monkey brains. Journal of Pharmacy and Pharmacology 24(5): 414-416 (May, 1972)

HO, B.T., McISAAC, W.M., WALKER, K.E. and ESTEVEZ. V. Inhibitors of monoamine oxidase. Influence of methyl substitution on the inhibitory activity of betacarbolines. Journal of Pharmaceutical Sciences 57(2): 269-273 (February, 1968)

A number of tetrahydro and aromatic beta-carbolines, mostly with a methyl substituent at various positions, were synthesized and their in vitro inhibitory activities on monoamine oxidase evaluated. Substitution of a methyl group at the N-9 nitrogen of metahydro-beta-carboline gave a potent competitive inhibitor of the enzyme. Methyl groups at C-1 of both tetrahydro and aromatic beta-carbolines generally reduced the potency, whereas introduction of a methyl group at the N-2 nitrogen of tetrahydro-beta-carboline gave a compound of equal activity.

HO, I.K., LOH, H.H. and WAY, E.L. Influence of 5,6-dihydroxytryptamine on morphine tolerance and physical dependence. European Journal of Pharmacology 21: 331-336 (1973)

The intracerebral administration of 5.6-dihydroxytryptamine (5,6-DHT) in the mouse inhibited the development of tolerance to and physical dependence on morphine induced by morphine pellet implantation. Reduction in tolerance development by 5,6-DHT was evidenced by the decreased amount of morphine necessary to produce analgesia and reduction in dependence development by the increase in the amount of naloxone necessary to induce precipitated withdrawal jumping in comparison with morphine-implanted animals receiving saline. Further evidence that 5,6-DHT reduced dependence development on morphine was evidenced by the fact that 5,6-DHT decreased the loss in body weight which occurred after abrupt morphine withdrawal. At the dose of 5,6-DHT used in this study (60 mu-g of the creatinine sulfate dihydrate 24 hr prior to morphine pellet implantation), the 5-HT level in the brain 4 days later was 75% of that of the control group while catecholamine levels remain unchanged. These studies substantiate the suggestion from this laboratory that central serotonergic system may be associated in the development of morphine tolerance and dependence.

HO, I.K., YAMAMOTO I., LOH, H.H. and WAY, E. L. Enhancement of pentobarbital responses after morphine addiction. The Pharmacologist 16(2): 193 (1974)

To assess the responses to pentobarbital in morphine dependence, ICR male mice were rendered dependent on morphine by pellet implantation for 3 days. On administering 75 mg/kg i.p. sodium pentobarbital, the sleeping time of such animals was found to be more than 2-fold longer than that of control animals implanted with a placebo pellet. The toxicity of pentobarbital in the morphine tolerant-dependent group was also increased, as evidenced by the decrease in LD50 of pentobarbital to 70% of that of the control group. In morphine pellet implanted mice, the activity of microsomal metabolizing enzyme, as measured by N-demethylation, was 35% inhibited. After a single dose of Na-pentobarbital, 60 mg/kg i.p., the brain levels of pentobarbital in the morphine group at 5, 15, 39 and 60 min were 35, 89, 41 and 99% higher, respectively, than that of the control group. Thus, it appears that the response to pentobarbital is enhanced after chronic morphinization and the effect may be attributed to increased brain uptake of pentobarbital after the development of tolerance and physical dependence on morphine.

HODGSON, J.R., BRISTOW, R.L. and CASTLES, T.R. Repression of RNA transcription during the development of analgesic tolerance to morphine. Nature 248(5450): 761-763 (April, 1974)

Following reports suggesting that ribonucleic acid (RNA) and protein synthesis are important for the development of morphine induced analgesic tolerance and dependency. the effect of chronic morphine drugging on the intracellular site of RNA synthesis -- nuclearchromatin -- was studied. It was found that brain chromatin from rats tolerant to morphine synthesized RNA more slowly than that from nontolerant rats. The results do not support any relationship between analgesia and brain chromatin template activity. It was further found that changes in brain chromatin template activity correlated chronologically with the onset and disappearance of morphine induced analgesic tolerance.

HODGSON, J.R., WOODHOUSE, E. J. and CASTLES, T.R. Brain chromatin template activity of rats treated with delta-9-tetrahydrocannabinol. Canadian Journal of Physiology and Pharmacology 51(5): 401-403 (1973)

Brain chromatin isolated from rats given a 10MG/KG intraperitoneal injection of delta-9-tetrahydrocannabinol exhibited a significantly lower capacity to promote RNA synthesis than chromatin from vehicle treated rats. The effect was not caused by either ribonuclease or an RNA polymerase inhibitor extracted with the chromatin.

HOLLISTER, L.E. Cannabidiol and cannabinol in man. Experientia 29: 825-826 (1973)

HOLLISTER, L.E. Human pharmacology of marihuana: What next? Psychopharmacology, Sexual Disorders and Drug Abuse. Edited by T. A. Ban, J.R. Boissier, G.J. Gessa, H. Heimann, L. Hollister, H.E. Lehmann, I. Munkvad, H. Steinberg, F. Sulser, A. Sundwall and O. Vinar. Amsterdam, the Netherlands: North-Holland Publishing Company, 1973. Pp. 705-706.

HOLLISTER, L.E. Marihuana in man. Three years later. Science 172: 21-28 (April, 1971)

The past 3 years of renewed research on the effects of marihuana in man has added little not previously known about the clinical syndromes produced by the drug. The major advance has been a quantification of dose in relation to clinical phenomena, and a beginning of an understanding of the drug's metabolism. The crucial clinical experiments in regard to the social questions about marihuana, such as the possible deleterious effects from chronic use, cannot be answered by laboratory experiments. These must be settled by close observations made on those who experiment on themselves. It should be possible, within a relatively short time, to determine whether marihuana has any medical utility, but the future would appear to be no more promising than the past in this regard. The mechanisms by which marihuana alters mental functions are not likely to be answered in man, nor even answered soon by animal studies. As marihuana may be unique among drugs in that more experimentation has been accomplished in man than in animals, it may be necessary to look to additional animal studies to provide leads for pertinent future studies in man.

HOLLISTER, L.E. Structure-activity relationships in man of cannabis constituents, and homologs and metabolites of delta-9-tetrahydrocannabinol. Experientia 11: 3-11 (1974)

Clinical studies of a variety of cannabis constituents and THC isomers, homologs and metabolites have elucidated some structure-activity relationships. The fundamental structure of THC is required for pharmacological activity. but potency may be altered greatly among different double-bond isomers, by changing length of side-chain or by metabolic hydroxylations. No material has been found in nature, either in cannabis itself or in the metabolites of THC, which differs qualitatively from THC.

HOLLISTER, L.E., KANTER, S.L., BOARD, R.D. and GREEN, D.E. Marihuana metabolites in urine of man. III. Unchanged delta-9-tetrahydrocannabinol. Research Communications in Chemical Pathology and Pharmacology 8(4): 579-584 (August 1974)

Positive identification of unchanged delta-9-tetrahydrocannabinol (THC) in the urine of man has been made following single oral doses of 30 mg in four subjects. Unchanged THC was found only in small amounts, approximately 0.01 - 0.005% of amount administered, and for only a few hours following drug administration.

HOLLISTER, L.E., KANTER, S.L., MOORE, F. and GREEN, D.E. Marihuana metabolites in urine of man. Clinical Pharmacology and Therapeutics 13(6): 849-855 (November-December, 1972)

Single closes of hashish extract containing 20 mg. of delta-9-tetrahydrocannabinol (THC) were followed by excretion of what appeared to be both cannabinol and cannabidiol but no unchanged THC. A new material in the urine appeared to be a compound related to a cannabinoid. The pattern of metabolism of cannabinoids appears to differ between different subjects. Following single doses of the same amount of THC alone, only a new drug-related metabolite could be found in the more polar range. With repeated dose a material in the cannabinoid range was excreted in small amounts. On the whole, repeated doses of hashish extract or THC as given in the present schedule did not lead to any significant accumulation of drug or metabolites.

HOLLISTER, L.E. and MOORE, F.F. Urinary catecholamine excretion after mescaline in man. Biochemical Pharmacology 17: 2015-2017 (1968)

HOLLISTER, L.E. and TINKLENBERG, J.R. Subchronic oral doses of marihuana extract. Psychopharmacologia 29: 247-252 (1973)

Subchronic oral doses of marihuana revealed no evidence of sensitization to the effects of two test doses of drug as compared to interval treatment with placebo. Slight evidence of tolerance to dizziness and tachycardia from the drug was noted, but not necessarily as a function of the amount of intervening drug exposure.

HORN, A.S. and SNYDER, S.H. Chlorpromazine and dopamine: Conformations-l similarities that correlate with the antischizophrenic activity of phenothiazine drugs. Proceedings of the National Academy of Sciences 68(10): 2325-2328 (October, 1971)

Phenothiazines and butyrophenones are known to alter dopamine (3,4-dihydroxyphenethylamine) metabolism in the brain in a fashion suggesting that they may block dopamine receptors. We observed, using Dreiding molecular models, that dopamine in its solid-state conformation is superimposable upon a portion of the known x-ray structure of chlorpromazine (2-chloro-10-(3-dimethylaminopropyl)-phenothiazine). The ability of phenothiazine drugs to mimic the dopamine-like conformation correlates with their antischizophrenic efficacy. These structure-activity relationships explain the importance of a substituent in ring a, a three-carbon side chain bearing the amino group, and a hetero atom between rings a and c.

HORN, A.S. and SNYDER, S.H. Steric requirements for catecholamine uptake by rat brain synaptosomes: Studies with rigid analogs of amphetamine. The Journal of Pharmacology and Experimental Therapeutics 180(3): 523-530 (1972)

The effects of cis - and trans-2-phenylcyclopropylamine and 1- and 2-amino-indanes, all rigid analogs of amphetamine, were examined for their ability to inhibit catecholamine uptake into synaptosomes from the hypothalamus and corpus striatum. Trans-2-phenylcyclopropylamine (tranylcypromine) was found to be a more potent inhibitor in both brain areas than the cis-isomer. Studies on the separate optical isomers of tranylcypromine showed that the (–)-isomer was more active than the (+) -form in both the hypothalamus and corpus striatum. 2-Aminoindane was a better inhibitor than 1-aminoindane in both regions of the brain. The above results suggest that the conformation of amphetamine at the catecholamine uptake site is with the side chain fully extended and the amino group above the plane of the ring, i.e., in an anti conformation. It is also suggested that knowledge of the differential antidepressant efficacy of (+)-and (–)-tranylcypromine might indicate the extent to which the drug's antidepresant activity is related to inhibition of monoamine oxidase activity or to impairment of catecholamine reuptake.

HUANG, J.T. and TAKEMORI, A.E. Accumulation of etorphine in rat brain slices. The Pharmacologist 16: 248 (August, 1974)

^{3}H-Etorphine (3. 3 Ci/mmole) was used to study the accumulation of this narcotic into slices of various brain areas. With 2 x 10^{-10}M etorphine in the medium, the T/M (tissue conc/medium conc) was significantly higher in slices of striatum (9.2) and thalamus 11.5) than in cortex (7.6) or fourth ventricular floor (8.2). However, the uptakes by slices of all brain areas were similar when 1.5 x 10^{-8}M etorphine was used. At very low conc of etorphine and using cortical and striatal slices, the uptake was saturable with maximum uptakes of 6.97 x 10^{-10} and 2.36 x 10^{-10} mole/gm/15 min respectively and uptake constants of 1.34 x 10^{-9} and 1.97 x 10^{-9} M respectively. At conc above 15 nM, the accumulation appeared to be nonsaturable. Dinitrophenol, fluoride, azide, iodoacetamide or Ca^{++} did not affect the saturable uptake of etorphine but N-ethylmaleimide or temperature of 0°C decreased the accumulation. Other organic bases such as hexamethonium or N-methylnicotinamide did not influence the uptake of etorphine. The saturable etorphine uptake was relatively stereospecific i.e. levorphanol was a more potent inhibitor of the uptake than dextrorphan. Etorphine uptake by brain slices from morphine-tolerant rats did not differ from that of non-tolerant rats.

HUANG, J.T. and TAKEMORI, A.E. Accumulation of methadone by choroid plexus in vitro. Neuropharmacology (in press)

HUG, C.C., JR. Characteristics and theories related to acute and chronic tolerance development. Chemical and Biological Aspects of Drug Dependence. Edited by S. Mule and H. Brill. Cleveland, Ohio: Chemical Rubber Company Press, 1972. Pp. 307-358.

IDANPAAN-HEIKKILA. J.E., FRITCHIE, G.E. and McISAAC. W.M. Pharmacological and behavioral studies of STP. Relationship to tissue distribution. Advances in Mental Science: Drug Dependence, Vol. 2. Austin, Texas: University of Texas Press, 1969. P. 24.

IWAMOTO, E.T., HO, I.K. and WAY, E.L. Elevation of brain dopamine during naloxone-precipitated withdrawal in morphine-dependent mice and rats. Proceedings of the Western Pharmacological Society 16: 14-18 (1973)

IWATSUBO, K. and CLOUET, D.H. The effects of narcotic analgesic drugs on the levels and the rates of synthesis of cAMP in six areas of rat brain. Federation Proceedings 32: 536 (1973)

The acute administration of narcotic analgesic drugs to experimental animals produces transient effects on both the levels and the rates of biosynthesis of biogenic amines in brain. The sensitivity of post-junctional elements to drug exposure has not been determined directly, although cAMP, has been shown to antagonize the analgetic effects of morphine. We have isolated synaptosomal membrane fractions from various areas of rat brain, and examined the effects of adding narcotic drugs on the adenylate cyclase activity of the preparations. At 1 mM concentration, morphine, levo- and dextro-methadone, levorphanol and dextrophan inhibited adenylate cyclase activity, by more than 50% in most areas. There was no stereospecificity, since the optical isomers, levorphanol and dextrorphan, were also equally inhibitory at 0.1 mM concentration. Unless the narcotic drugs are concentrated at the synaptic membrane, it is unlikely that the drug concentration in vivo would be high enough to be inhibitory. The levels of cAMP were measured in the same brain areas removed from rats killed by microwave irradiation after the injection of morphine in acute dose. The levels of the 'second messenger' tended to decrease during the period two hours after drug administration, with significant decreases in cAMP levels in homogenates of medulla and hypothalamus.

JATLOW. P. Ultraviolet spectrophotometric analysis of drugs in biological fluids. American Journal of Medical Technology 39(6): 231-236 (June, 1973)

For abstract, see Section I. Methodology of Drug Research.

JOHNSON, C.L., KANG, S. and GREEN, J.P. Conformational analysis by a combined molecular-orbital-classical procedure. Conformation of Biologiccal Molecules and and Polymers, the Jerusalem Symposia on Quantum Chemistry and Biochemistry, Vol. V. Jerusalem, Israel: The Israel Academy of Sciences and Humanities, 1973. Pp. 517-529.

JOHNSON, J. C. and CLOUET, D.H. Studies on the effect of acute and chronic morphine treatment on catecholamine levels and turnover in discrete brain areas of rats. Federation Proceedings 32: 757 (1973)

For acute studies, male, Sprague-Dawley rats received 5, 20, or 60 mg/kg morphine (M) base s.c. and were sacrificed 15, 30, or 60 min after treatment. For chronic studies rats received 60 mg/kg daily for 5 days and were sacrificed 60 min after the 5th injection, or rats were implanted with an M pellet. Ten min before sacrifice all rats received 5 mu-g ^{14}C-tyrosine (T) intracisternally. Brains were removed and dissected into 6 areas: 1) cerebellum, 2) medulla, 3) hypothalamus, 4) striatum, 5) midbrain and 6) cortex. The levels of dopamine (DA) norepinephrine (NE) and T were measured fluorimetrically and the incorporation of ^{14}C-T into the amines determined by liquid scintillation spectrometry. With acute M treatment NE levels decreased at 30 min and returned to normal or above normal values by 60 min in all brain areas while DA was decreased at 30 min and normal at 60 min in area 4. With chronic treatment NE levels remained decreased in areas 2 and 5 and elevated in areas 3 and 6 while DA levels were elevated in area 4. T levels and T specific activity were found not to change significantly with acute or chronic M treatment. NE synthesis was decreased by acute M treatment in areas 3 and 4 while DA synthesis was increased in areas 2,3,4 and 5. Chronic M treatment decreased NE synthesis in area 3 and elevated DA synthesis in all areas studied.

JONAS, W. and SCHEEL-KRÜGER. J. Amphetamine induced stereotyped behavior correlated with the accumulation of O-methylated dopamine. Archives internationales de Pharmacodynamie et de Therapie 177: 379-389 (1969)

Amphetamine provokes in rats pretreated with reserpine a marked central excitation: The initial locomotor activity is followed by a phase with a characteristic stereotyped behaviour consisting of sniffing, licking and gnawing.

Biochemical analyses were performed of the brain amines depamine, noradrenaline and their respective O-methylated metabolites 3-methoxytyramine and normetanephrine.

In rats pretreated with the monoamincoxidase-inhibitor nialamide only, amphetamine induced an increased accumulation of both 3-methoxytyramine and normentanephrine.

An additional dose of reserpine clarified that amphetamine still provoked a significantly increased accumulation of 3-methoxytyramine correlated with the stereotyped behaviour while the levels of the other brain amines were decreased to undetectable low levels.

Hyperthermia was excluded as a causative factory for this isolated metabolic effect of amphetamine.

The result thus seems to indicate that the amphetamine induced stereotyped behaviour in these reserpinized rats is correlated with an increased turnover of dopamine.

JONES, R. Significance and characteristics, of drug dependence: Characteristics of drug dependence to cannabis. Chemical and Biological Aspects of Drug Dependence. Edited by S.J. Mule and H. Brill. Cleveland, Ohio: Chemical Rubber Company Press, 1972. Pp. 65-81.

JUCHAU, M.R. and HORITA, A. Metabolism of hydrazine derivatives of pharmacologic interest. Drug Metabolism Reviews 1(1): 71-100 (1972)

Hydrazine and its derivatives represent a group of highly reactive chemicals which are utilized extensively for many varied purposes. They are capable of producing a wide spectrum of biological effects, some of which are useful therapeutically, others of which are definitely harmful. The manner and rate of biotransformation of these compounds play a major role in determining the nature of the observed effects. Acetylation appears to be the most important mode of biotransformation with respect to inactivation of such compounds, whereas hydrolysis, oxidation, and reduction frequently result in the formation of metabolites with potent biological effects. Biotransformation appears to be essential to the capacity of many of these compounds to inhibit monoamine oxidase. Conversion to substances which contain a free $-NH_2$ group is frequently requisite to inhibition of this important enzyme system. Other biotransformation reactions tend to terminate the inhibitory effect on monoamine oxidase but may result in the formation of compounds which inhibit other biochemical systems.

KAIKO, R.F. and INTURRISI, C.E. Human biotransformation and exertion of orally administered cyclazocine: A method and its application. The Pharmacologist 15(2) (Fall, 1973)

For abstract, see Section I. Methodology of Drug Research.

KAIKO, R.F. and INTURRISI, C.E. The quantitation of cyclazocine and its metabolities in human urine by use of gas-liquid chromatography. Journal of Chromatography 100: 63-72 (1974)

For abstract, see Section I. Methodology of Drug Research.

KANDEEL, E.M., ANDERSON, L. J., BLOCK, J.H., WHITE, A.I. and MARTIN, A.R. Substituted tetralins IV: Synthesis and stereochemistry of 4,4-disubstituted 1,2,3,4-tetrahydro-2-naphthoic acids. Journal of Pharmaceutical Sciences 61(8): 1231-1234 (August, 1972)

The syntheses of four 4-methyl-4-phenyl-1,2,3,4-tetrahydro-2-naphthoic acids are described. The sterospecific cyclization of the cis-isomers and proton NMR studies establishing cis-trans product rations are also reported.

KANDEEL, E.M. and MARTIN, A.R. Substituted tetralines. 5. Analgesic properties of some diastereoisomeric N, N-dimethyl-4-phenyl-1,2,3,4 -tetrahydro-2-naphthylamines. Journal of Medicinal Chemistry 16: 947-948 (1973)

KANG, S. Conformation and electronic structures of pilocarpine, a muscarinic agonist. International Journal of Quantum Chemistry: Quantum Biology Symposium 1: 109-117 (1974)

The electronic structures and conformations of pilocarpine, a muscarinic agonist, have been studied by the INDO molecular orbital method and the classical potential function method.

A conformation of pilocarpine congruent with other potent muscarinic agonists was observed in the allowed conformational energy range. This conformation is near psi = 60° and theta = 260°. It is suggested that the lower muscarinic agonist potency of pilocarpine relative to acetylcholine is probably due to the lower $_pK_a$ value ($_pK_a$ = 6.07) of the imidazole ring nitrogen. rather than to the molecular conformation.

KANG, S. and GREEN, J.P. Steric and electronic relationships among some hallucinogenic compounds. Proceedings of the National Academy of Sciences 67(1): 62-67 (September, 1970)

Stereochemical considerations and total valence electron calculations suggest congruities among the ostensibly dissimilar hallucinogenic compounds, D-lysergic acid diethylamide (LSD), indolealkylamines, and methoxylated amphetamines. In LSD the aromatic benzene ring A and the N-6 nitrogen are essential for hallucinogenic activity; these sites may react with the receptor. The conformations of amphetamines and indolealkylamines at the receptor are such that the aromatic benzene ring lies like ring A of LSD and the alkylamino nitrogen lies like the N-6 of LSD. Ring A may interact with the receptor by forming a pi-molecular complex, as suggested by the correlation between hallucinogenic activity and energy of the highest occupied molecular orbital (E_H) of congeneric series. The N-6 nitrogen of LSD and the sterically congruent nitrogen of the other hallucinogenic compounds may react with the receptor by forming a donor acceptor complex of the n-psi or n-rho type. Other portions of the hallucinogenic molecules confer a favorable E_H: these include the methoxy and hydroxyl groups of the amphetamines (and mescaline), and the indolealkylamines; and the pyrrole ring of LSD and the indolealkylamines.

KANG, S., JOHNSON, C.L. and GREEN, J.P. The conformation of 5-hydroxytryptamine. Journal of Molecular Structure 15: 453-457 (1973)

KANG, JOHNSON, C.L. and GREEN, J.P. Theoretical studies on the conformations of psilocin and mescaline. Molecular Pharmacology 9(5): 640-648 (September, 1973)

Molecular orbital calculations and classical potential function calculations were carried out to examine the proposal that the conformations of the hallucinogenic tryptamines and phenylalkylamines are such that their 6-membered aromatic rings and their alkylamino nitrogens are congruent with the A ring and N(6) nitrogen atom of lysergic acid diethlamide (the nitrogen of the D ring). The congruent conformation of psilocin is psi[C(9)--C(3)--C(beta)--C(alpha)]= 46 ± 10 degrees, alpha [C(3) C(beta)--C(alpha)--N]= 230 ± 20 degrees, $theta_1$[C(beta)--C(alpha)--N--C(1N)] = 180 ± 10 degrees, and $theta_2$[C(beta)--C(alpha)--N--C(2N)= 300 ± 10 degrees; that of mescaline is psi[C(2)--C(1)--C(beta)--c(alpha)] 147 ± 10 degrees and eta[C(1)--C(beta)--C(alpha)--N]= 160 ± 20 degrees. These results show that congruence of psilocin and mescaline with lysergic acid diethylamide is energetically permissible.

KANTER, S.L., HOLLISTER, L.E., MOORE, F. and GREEN. D.E. Marihuana metabolites in urine of man. IV. Extraction procedures using diethyl ether. Research Communications in Chemical Pathology and Pharmacology 9(2): 205-213 (October, 1974)

For abstract, see Section I. Methodology of Drug Research.

KANTER, S.L., HOLLISTER, L.E., MOORE, F. and GREEN, D.E. Marihuana metabolites in urine of man. II. Underscribed metabolite following oral ingestion of delta-9-tetrahydrocannabinol. Research Communications in Chemical Pathology and Pharmacology 7(1): 79-84 (January, 1974)

A major metabolite derived from the metabolism of THC administered orally to man has been detected by an improved thin-layer chromatographic technique. It appears in the urine within the first 12 hours following the drug and persists for at least 36 hours. By various types of exclusion, it is not the 11-hydroxy, 8-beta-hydroxy, 8-alpha-hydroxy, or 8, 11-dihydroxy metabolite of delta-9-THC.

KARLER. R., CELY, W. and TURKANIS, S.A. Anticonvulsant activity of delta-9-tetrahydrocannabinol and its 11-hydroxy and 8-alpha, 11-dihydroxy metabolites in the frog. Research Communications in Chemical Pathology and Pharmacology 9(3): 441-452 (November, 1974)

In the frog (Rana pipiens) delta-9-tetrahydrocannabinol (delta-9-THC) exhibits pronounced anticonvulsant activity against maximal electroshock. A study of the metabolic fate of ^{3}H-delta-9-THC demonstrated that delta-9-THC is rapidly metabolized to several unidentified metabolites, as well as to mono- and dihydroxylated products; brain amounts of both the hydroxylated metabolites and delta-9-THC were measured as a function of time, but none of these measurements correlated quantitatively with the time course of anticonvulsant activity. Both 11-hydroxy- and 8-alpha, 11-dihydroxy-delta-9-THC metabolites displayed anticonvulsant activity. All the cannabinoids tested were much more potent in the frog than in the rat or mouse; but there was no such disparity in the potency of diphenylhydantoin and phenobarbital in the different species. The unanticipated pharmacological activity of the metabolite, 8-alpha, 11-dihydroxy-delta-9-THC, emphasizes the complexity of delta-9-THC and its numerous effects.

KHANNA, K.L., ROSENBERG, H. and PAUL, A.G. Biosynthesis of mescaline. Chemical Communications. 1969. London, England: The Chemical Society, 1969. P. 315.

A pathway of biosynthesis of mescaline from 3,4-dihydroxy phenethylamine via m-O-methylation is proposed.

KHANNA, K.L., TAKIDO, M., ROSENBERG, H. and PAUL, A.G. Biosynthesis of phenolic tetrahydroisoquinoline alkaloids of peyote. Phytochemistry 9: 1811-1815 (1970)

Data are presented supporting a proposed pathway of biosynthesis of the phenolic tetrahydroisoquinoline alkaloids of peyote from dopamine. It is suggested that meta-O-methylation of dopamine, hydroxylation in the 5-position. para-O-methylation and finally cyclizations yield anhalamine, anhalidine, anhalonidine and pellotine.

KIDD, M.R., ELLIS, R.D. and CAUTHEN. S.E. The properties of fractionated rabbit serum cocainesterase. Presented at the American Chemical Society 28th Southwest Regional Meeting, Baton Rouge, Louisiana, December 6-8, 1972.

Cocainesterase has been purified 334-fold from commercially available, pooled rabbit serum using the following methods: ammonium sulfate fractionation, Sephadex G-75 gel filtration, elution from QAE-Sephadex using a linear gradient of from 0.1 to 0.4 N KCl in phosphate buffer, and elution from alumina Cgamma gel. The enzyme was assayed by following the titration of acid produced upon hydrolysis. The yield of the most highly purified preparation was about 50% and its specific activity was 0.32 mu-moles base uptake/min/mg protein. Michaelis constants were determined for cocaine and tropacocaine with the purified enzyme and found to be 1.7×10^{-4}M and 3.9×10^{-4}M respectively. Also, the following compounds were tested as possible substrates: atropine sulfate, atropine methyl bromide, scopolamine HBr, acetyl-beta-methyl choline chloride, pilocarpine HCl, hyoscyamine sulfate, and eucatropine HCl. The purified preparation was tested for other esteratic activities known to be present in rabbit serum. Acetylcholinesterase was shown to be absent from the purified enzyme and shown to be separated from it in the gel filtration step: atropinesterase activity was separated from cocainesterase on the ion-exchange column. However, activity with phenyl acetate, tributyrin and phenyl butyrate was observed.

KINZER, G.W., FOLTZ, R.L., MITCHELL, R.I., BATTELLE and TRUITT, E.B., JR. The fate of the cannabinoid components of marihuana during smoking. Bulletin on Narcotics 26(3): 41-54 (July-September, 1974)

Cannabis of known origin was used to prepare cigarettes, The cigarettes were smoked by machine under conditions which simulated the smoking patterns of a typical marihuana smoker. Both the smoke condensate and the marihuana plant extract were analyzed by gas chromatography and mass spectrometry. It was found that approximately 50 per cent of the delta-9-tetrahydrocannabinol in the marihuana was destroyed during the smoking process. Analysis for the cannabinoid acids was achieved by trimethylsilylation followed by gas chromatography. The trimethylsilylated cannabinoids were identified on the basis of their mass spectra. Some of the delta-9-tetrahydrocannabinolic acid and the cannabidiolic acid were found to survive the smoking process.

KNAPP, S., MANDELL, A.J. and GEYER. M.A. Effects of amphetamines on regional tryptophan hydroxylase activity and synaptosomal conversion of tryptophan to 5-hydroxytryptamine in rat brain. The Journal of Pharmacology and Experimental Therapeutics 189(3): 676-689 (1974)

The acute administration of d-amphetamine, methamphetamine p-chloroamphetamine. and l-amphetamine reduced the conversion of tryptophan to serotonin (5-HT) in synaptosomes from the rat striatum. d-Amphetamine was approximately twice as potent as l-amphetamine in decreasing conversion activity. In contrast, fenfluramine increased this index of nerve ending 5-HT biosynthesis. None of the amphetamines studied affected synaptosomal uptake of ^{14}C-L-tryptophan when measured in the same tissue preparations in which conversion activity was studied. The activity of solubilized tryptophan hydroxylase in the striatal synaptosomes was decreased by d-amphetamine treatment to the same extent that conversion activity was, accounting for the decrease in conversion activity. Tryptophan hydroxylase activity in the lateral midbrain after d-amphetamine was decreased to the same extent that it was in the nerve ending, but the decrease in the lateral midbrain preceded that observed in the nerve ending. Enzymic activity in the medial midbrain area was unaffected by d-amphetamine. At a concentration of 100 mu-M none of the amphetamines studied had a demonstrable effect on tryptophan hydroxylase activity in vitro. At 100 mu-M in vitro and 10 mg/kg in vivo, the two major amphetamine metabolites in the rat, p-hydroxyamphetamine and p-hydroxynorephedrine, failed to influence regional tryptophan hydroxylase activity or synaptosomal conversion of tryptophan to 5-HT. The short latency of the amphetamine-induced changes in nerve ending 5-HT synthetic activity contrasts with the delay of days to weeks in response to such agents as lithium and morphine as we have previously reported.

KOKOSKI, R.J., SANDS, F.L. and KURLAND. A.A. Morphine detection by thin-layer chromatography in a urine-screening program. A comparison of ion-exchange-resin loaded paper extraction with direct solvent extraction. Committee on Problems of Drug Dependence, 1969. Washington, D.C.: National Academy of Sciences, National Research Council, 1969.

KRUMHOLZ, W.V., SHEPPARD, C. and MERLIS, S. Clinical evaluation of butaperazine (AHR 712). Current Therapeutic Research 9(4): 220-224 (April, 1967)

Twenty-four male chronic psychotic patients with an average age of 39 years and an average duration of overt illness of 11 years were given butaperazine, a new antipsychotic drug, for a period of 12 weeks in doses between 10 mg. and 100 mg. daily. The optimal therapeutic dose seemed to be around 30 mg. daily. Extrapyramidal disturbances were observed in 16 patients at different dose levels. At higher dose levels, minor non-extrapyramidal side effects were observed.

Laboratory tests revealed no significant pathological changes.

Five patients showed interesting positive behavior changes and were continued for another 24 weeks on butaperazine. The authors remained with the impression that butaperazine may have some value in the treatment of chronic schizophrenic patients.

KUBENA, R.K., PERHACH, J.L., JR. and HERBERT, B., III. Corticosterone elevation mediated centrally by delta-1-tetrahydrocannabinol in rats. European Journal of Pharmacology (14)1: 89-92 (1971)

Assays of peripheral plasma corticosterone, 45 minutes after intraperitoneal injection of 2 to 16 mg/kg of delta-1-tetrahydrocannabinol, showed strong pituitary adrenal activation which persisted undiminished after a week of daily doses. Experiments were performed on a total of 230 male albino rats. Blockage of the steroid activation, by hypophysectomy or by pretreatment with pentobarital and morphine, indicated a hypothalmic or other central locus of this action of delta-1-tetrahydrocannabinol. (Author Abstract Modified)

KUCZENSKI, R. Effects of catecholamine releasing agents on synaptosomal dopamine biosynthesis: Multiple pools of dopamine or multiple forms of tyrosine hydroxylase? Neuropharmacology (in press)

The effects of agents, which are known to induce release of catecholamines from synaptosomes, were assessed on the synthesis of dopamine from tyrosine. as reflected in the evolution of $^{14}CO_2$ from L-(1-^{14}C) - tyrosine, in intact rat striatal synaptosomes. At a time when release has occurred, whereas reserpine inhibits the synthesis of dopamine from tyrosine, with an ED_{50} of 1 x 10^{-8} M, tyramine (ED_{50} of 1 x 10^{-5} M) and amphetamine (ED_{50} of 1.4 x 10^{-6} M) enhance the rate of synthesis. The presence of nialamide (10^{-4} M) or pargyline (10^{-3}M) has no effect on synaptosomal dopamine synthesis in the absence or presence of amphetamine, tyramine, or reserpine. Neither reserpine, tyramine, nor amphetamine affect the activity of tyrosine hydroxylase or dopa decarboxylase in the absence of synaptosomal structural integrity. Nor do these drugs affect the accumulation of ^{3}H-tyrosine into synaptosomes. The data are consistent with the existence of at least two pools of synaptosomal dopamine, one of which can interact with tyrosine hydroxylase. Two hours after pretreatment of rats with 5 mg/kg D-amphetamine, the level of synaptosomal dopamine biosynthesis is decreased by 39%. The rate of dopamine synthesis in synaptosomea from amphetamine-pretreated rats was assessed in the presence of reserpine and tyramine. The data are not consistent with alterations in pool size as the only mechanism affecting synaptosomal dopamine synthesis. A mechanism is discussed involving an equilibrium of tyrosine hydroxylase between active and inactive conformers in the presence of an inhibitory pool of dopamine.

KUCZENSKI, R. Striatal tyrosine hydroxylases with high and low affinity for tyrosine: Implications for the multiple-pool concept of catecholamines. Life Sciences 13: 247-255 (1973)

Synaptic membrane-bound tyrosine hydroxylase from rat striatum exhibits a decreased Km for cofactor and a decreased Km for substrate over values obtained for the soluble enzyme. The proximity of this fraction of the catecholamine biosynthetic apparatus to the probable site of neurotransmitter release and its higher affinity for substrate provide for a mechanism by which newly synthesized transmitter may be preferentially released.

KUHAR, M.J., SHASKAN, E.G. and SNYDER, S.H. The subcellular distribution of endogenous and exogenous serotonin in brain tissue: Comparison of synaptosomes storing serotonin. norepinephrine, and gamma-aminobutyric acid. Journal of Neurochemistry 18: 333-343 (1971)

We have studied the subcellular distribution of exogenous and endogenous serotinin in slices from the hypothalamus and midbrain of several species. In a procedure which appears to label the endogenous pools, tissue slices were incubated with low concentrations of (^{3}H)5-HT (5 x 10^{-8}M), for 45 min, when there was apparent equilibrium between (^{3}H)5-HT of tissue and medium. After the tissue slices were homogenized in 0.32 M-sucrose and subjected to differential centrifugation. the distribution of exogenous and endogenous 5-HT in pellets and supernatant fluid was similar.

In some experiments, the crude mitochondrial pellets were resuspended in 0.32 M-sucrose, layered on linear, continuous density gradients of sucrose (1.5-0. 32M), and centrifuged for short times (incomplete equilibrium centrifugation). The subcellular distribution of particulate tritium, total tritium, and particulate endogenous 5-HT was the same in portions of the gradients containing synaptosomes. The peak distribution of (^{3}H)5-HT in sucrose gradients was separable from the peak for (^{14}C)GABA by four to five fractions; potassium (a marker for cytoplasm occluded within synaptosomes) occurred in the regions of the gradients containing most of the labelled compounds. The distribution of monoamine oxidase activity (a mitochondrial marker) overlapped the distribution of (^{3}H)5-HT after a 15 min centrifugation but appeared in denser regions of the gradient after centrifuging for 2 h. Particles containing (^{3}H)5-HT and (^{14}C)NE were slightly but consistently separable in synaptosomal fractions isolated from the hypothalamus or midbrain of rat, guinea pig and hamster.

KUHN, C.M. and SCHANBERG, S.M. Metabolism of D-amphetamine by rat brain in vivo and in vitro. The Pharmacologist 16: 228 (1974)

The ability of brain tissue to hydroxylate amphetamine (A) to p-hydroxyamphetamine (P) and norephedrine (N) is the subject of some controversy, although the metabolism of A to P and p-hydroxynorephedrine (PNE) has been demonstrated in some organs of the rat. To study this problem, brain slices were incubated with tritiated (^{3}H) A for one hour. Metabolites were extracted. dansylated and then separated by TLC. At lower concentrations of A, only P and PNE were identified, but at the higher concentration N also could be isolated. In addition rats were injected intracisternally with ^{3}H-A, and A and metabolites were isolated at various times after injection. P, N and PNE could be isolated 15 min. after injection. However, while the concentration of P and N declined rapidly over 4 hours the amount of PNE increased gradually during this same period. Brains obtained from animals injected i.p. with the same dose of ^{3}H-A did not contain measurable levels of hydroxylated metabolites. These data suggest that A can be metabolized to P and NE by rat brain tissue.

KULLBERG, M.P. and GORODETZKY. C.W. Studies on the use of XAD-2 resin for detection of abused drugs in urine. Clinical Chemistry 20(2): 177-183 (1974)

For abstract, see Section I. Methodology of Drug Research.

KULLBERG, M.P., GORODETZKY, C.W. and CONE, E.J. Identification of etorphine (E) in human urine after a single 100 mu-g dose. The Pharmacologist 16(2): 193 (Fall, 1974)

Urine was collected for 24 hrs. prior to and following subcutaneous administration of 100 mu-g E to 4 drug-free subjects. Post-drug samples were combined into single 24-hour samples for 3 subjects and two 12 - hour samples for one subject, and analyzed as follows: 1. The two 12-hour samples were extracted on an XAD-2 resin column, eluted with $CHCl_3$, concentrated, extracted with 1N HCl, adjusted to pH 8.5 and reextracted with $CHCl_3$, evaporated to dryness and redissolved in 100 mu-l of ethyl acetate: 2. two 24-hour samples were extracted on XAD-2 resin colums. eluted with $MeOH/H_2O/NH_4OH$, evaporated to dryness, redissolved in H_2O, subjected to beta-glucuronidase nycrolysis, extracted with $CHCl_3$ then 1N HCl and then $OHCl_3$. and finally evaporated to dryness and redissolved in ethyl acetate: 3. one 24-hour sample was subjected to beta-glucuronidase hydrolysis then extracted as in 1. Urine extracts were analyzed for E with a Finnigan 1015D GC/MS using mass fragmentography to monitor the two major ions at m/e 413(M+l) and 395[(M+1) -18] by methane chemical ionization. E was detected in all post-drug urine extracts by occurrence of the major ions, ion ratios, and retention time compared to authentic E and extracts of pre-drug control urine. The sensitivity for detection of pure E was 5-10 ng.

KUPFER. D., LEVIN, E. and BURSTEIN, S.H. Studies on the effects of delta-1-tetrahydrocannabinol (delta-1-THC) and DDT on the hepatic microsomal metabolism of delta-1-THC and other compounds in the rat. Chemico-Biological Interactions 6: 59-66 (1973)

LABRECQUE, G. and DOMINO, E.F. Tolerance to and physical dependence on morphine: Relation to neocortical acetylcholine release in the cat. The Journal of Pharmacology and Experimental Therapeutics 191: 189-200 (1974)

LANG, D.W., DARRAH, H.K., HEDLEY-WHYTE, J. and LAASBERG, L.H. Increased ^{35}S-methionine in brain of morphine addicted rats. Federation Proceedings 33: 1486 (1974)

Effect of morphine (MS) on protein synthesis in rat brain was evaluated in tolerant and acute rats. Male Wistar-Lewis rats were randomly divided to control, tolerant and acute groups (N=10). The rats were made tolerant by giving MS (25 mg/kg b.i.d.) for either 42 or 84 d. An aqueous solution of ^{35}S methionine (0.5 mu-C/gbw) was administered IV. All groups were then sacrificed at 20 min., 1 hr and 2 hrs after ^{35}S-methionine IV. The ^{35}S-activity in TCA precip proteins and supernate from cortex, hypothalamus, putamen, corpus callosum, thalamus, cerebellum, kidney and liver was determined. In addition the activity of label in lipid, saline soluble and insoluble proteins of whole brain for tolerant and control (N=12) rats was determined. The ^{35}S-activity in brain proteins of acute rats did not differ from those of controls. The six brain areas in tolerant rats after 1 and 2 hrs injection of ^{35}S-methionine showed a 15%, then 30% increase in activity (dpm/mg protein). Proteins from putamen and corpus callosum had w/w 60% of the ^{35}S-activity found in hypothalamus and cortex. There was no difference in ^{35}S-activity in kidney and liver of control and tolerant rats. The activity of the label in brain lipids was 2% of that found in proteins in both tolerant and control groups. Protein synthesis in morphine tolerant rat brain is significantly (less than 0.01) increased as judged by incorporation of ^{35}S-methionine.

LAWRENCE, R.H., JR. and WALLER, G.R. GC-MS/Probe-MS analysis of cannabinoid in resin glands of Cannabis sativa L. Presented at the 13th Annual Meeting of the Phytochemical Society of North America, Pacific Grove, California, 1973. P. 24.

For abstract, see Section I. Methodology of Drug Research.

LAWRENCE, R.H., JR. and WALLER, G.R. Glandular structures of Cannabis sativa L. and cannabinoid production. Presented at the 50th Annual Meeting of the American Society of Plant Physiologists, Cornell University, Ithaca, New York. Plant Physiology 53: s-13 (1974)

For abstract, see Section I. Methodology of Drug Research.

LAWRENCE, R. H., JR. and WALLER, G.R. The role of specialized epidermal gland in the production of cannabinoids in Cannabis sativa L. Proceedings of the 9th IUPAC International Symposium on Chemistry of Natural Products, Ottawa, Canada, Abstract 24C, 1974.

For abstract, see Section I. Methodology of Drug Research,

LAWRENCE, R.H., JR., WALLER, G.R. and KINNEBERG, K.F. An improved method of sample introduction in gas chromatography-mass spectrometry of biological materials. Analytical Biochemistry 62(1): 102-107 (November, 1974)

For abstract, see Section I. Methodology of Drug Research.

LEMBERGER. L., MARTZ, R., RODDA, B., FORNEY, R. and ROWE, H. Comparative pharmacology of delta-9-tetrahydrocannabinol and its metabolite, 11-OH-delta-9-tetrahydrocannabinol. Journal of Clinical Investigation 52(10): 2411-2417 (October, 1973)

A comparison of the psychologic and physiologic effects of intravenously administered delta-9-tetrahydrocannabinol (delta-9-THC) and 11-hydroxy-delta-9-tetrahydrocannabinol (11-OH-delta-9-THC) was carried out in nine casual marihuana smokers. A marked tachycardia and psychologic "high" occured within 3-5 min after the i.v. administration of 11-OH-delta-9-THC (1 mg) to all subjects. In contrast, the peak psychologic "high" was delayed 10-20 min after the i.v. administration of delta-9-THC (1 mg). There was some individual variation in response among subjects. Psychologic effects correlated well with plasma levels of unchanged (^{3}H)11-OH-delta-9-THC. About 75% of the administered radioactive dose was excreted in urine (25%) and feces (50%) after (^{3}H)11-OH-delta-9-THC administration. The disposition, excretion, and metabolism of (^{3}H)11-OH-delta-9-THC appear to be similar to that previously reported after (^{14}C)delta-9-THC administration. These findings, in conjunction with the marked psychologic high seen after 11-OH-delta-9-THC, suggest that in man, delta-9-THC, the active constituent in marihuana, is converted to 11-OH-delta-9-THC, which is in part responsible for the psychologic effects.

LEMBERGER, L., SILBERSTEIN, S.D., AXELROD, J. and KOPIN, I.J. Marihuana: Studies on the disposition and metabolism of delta-9-tetrahydrocannabinol in man. Science 170: 1320-1322 (December, 1970)

LEMBERGER. L., TAMARKIN. N.R., AXELROD, J. and KOPIN, I.J. Delta-9-tetrahydrocannabinol: Metabolism and disposition in long-term marihuana smokers. Science 173: 72-74 (July, 1971)

Radioactively labeled delta-9-tetrahydrocannabinol (delta-9-THC) administered intravenously to chronic marihuana smokers disappeared from the blood plasma with a half-life of 28 hours as compared to 57 hours for nonusers of marihuana. Apparent volumes of distribution did not significantly differ between the two groups. Within 10 minutes after administration of delta-9-THC, 11-hydroxy-delta-9-THC is present in the plasma of nonusers and chronic users. This metabolite was also present in urine and feces of nonusers and long-term marihuana smokers. In addition, polar metabolites were excreted in urine and feces of both groups for more than 1 week.

LIN, S.C., SUTHERLAND, V.C. and WAY, E.L. Brain amino acids in morphine tolerant and non-tolerant rats. Proceedings of the Western Pharmacological Society 16: 8-13 (1973)

LINDER, C. and FISHMAN, J. Narcotic antagonists. 1. Isomeric sulfate and acetate esters of naloxone (N-allylnoroxymorphone). Journal of Medicinal Chemistry 16(5): 553-556 (1973)

For abstract, see Section I. Methodology of Drug Research.

LIRAS, P., ATHENHOLT, T. and UMBRECHT, W.W. Microbial transformations of morphine by bacteria. Developments in Industrial Microbiology (in press)

LOEW, G.B. and JESTER, J.R. Quantum chemical studies of meperidine and prodine. Journal of Medicinal Chemistry (in press)

Extensive quantum chemical calculations have been made of the conformational behavior of meperidine, desmethyl. alpha ± beta ± prodine, using PCILO, a semi-empirical molecular orbital method. For this series of opiates. a phenyl-equatorial conformation was preferred over a phenyl-axial one, with the equatorial conformer most favored in the most potent compounds.

Using the low energy equatorial conformer obtained for each compound, we were able to successfully account for their observed potency variation. We could further deduce that a flexible phenyl, rather than piperidine, ring site was probably involved in accommodation of these compounds at the morphine receptor.

LOEW, G.H. and BERKOWITZ, D.S. Quantum chemical studies of morphine-like opiate narcotics: Effect of N-substituent variations. Journal of Medicinal Chemistry (in press)

Quantum chemical calculations including extensive conformational variations are performed on three morphine-like analgesics with varying N-substituents using the PCILO and INDO methods. The three compounds, morphine, nalorphine, and N-phenethyl-morphine have been shown experimentally to exemplify opiate narcotic agonism, antagonism, and increased agonism respectively. In this study, these properties are correlated with the electronic and conformational results. The electronic properties of the fused ring skeleton including specifically the cationic region around the nitrogen are relatively unaffected by varying N-substituents. The properties studied include net charges, bond polarities, and the nature and energy of the highest filled and lowest empty molecular orbitals. The conformationai behavior appears to be the main cause of differing receptor binding and interaction with the active site and is discussed in these terms.

LOH, H.H., HITZEMANN, R.J. and WAY, E.L. Effect of acute morphine administration of the metabolism of brain catecholamines. Life Sciences 12(Part I): 33-41 (1973)

The effects of sub-analgetic and analgetic doses of morphine (5-20 mg/kg) on the metabolism of intravenously administered (^{14}C)-tyrosine (200 uCi/kg) in the mouse brain were investigated. A significantly increased conversion of (^{14}C)-tyrosine to the (^{14}C)-catecholamines was observed only at an analgetic dose of morphine. Furthermore, morphine increased the specific activity of brain (^{14}C)-tyrosine and this effect was blocked by naloxone. a morphine antagonist.

LOMAX, P., GROSS, S.J. and CAMPBELL, C. Immunological blockade of the hypothermic effect of delta-9-tetrahydrocannabinol in the rat. Pharmacology of Thermoregulation. Edited by E. Schenbaum and P. Lan. Basel, Switzerland: Karger, 1973. Pp. 488-490.

LOPATIN, D.E., WINKELHAKE, J.L. and VOSS, E.W., JR. Immunochemical characterization of lysergyl derivative incorporated into protein. Molecular Pharmacology 10(5): 767-775 (September, 1974)

A derivative of d-lysergic acid diethylamide (LSD), lysergyl$_{der}$, previously shown to be covalently coupled to secreted low molecular weight peptides, was shown during incubation in vitro of immune lymphoid cells with LSD to possess structural features closely resembling the parent molecule. Binding studies of LSD and lysergyl$_{der}$ ligands with antibodies directed against both lysergic acid and lysergyl$_{der}$ suggested that both antibodies possessed similar specificity. (^{3}H)LSD and (^{3}H)lysergyl$_{der}$ were bound by anti-lysergyl antibody with average intrinsic a-sociation constants (K_o) of 3.5 X 10^5 M^{-1} and 7.8 X 10^5 M-1, respectively. Both ligands were bound by anti-lysergyl$_{der}$ antibody with K_o values of 1-2 X 10^5 M^{-1}. Single-point equilibrium dialysis experiments indicated that both antibody populations bound the derivative in preference to LSD. Mild alkaline hydrolysis of LSD was shown to generate a molecular species which was bound by anti-lysergyl$_{der}$ antibody with the same energy as lysergyl$_{der}$. Alkaline hydrolysis had no effect on lysergyl$_{der}$. These data suggest generation of a demethylated derivative of LSD during incubation of LSD in vitro.

LYNN, R.K., SMITH, R., OLSEN, G.D., LEGER, R.M. and GERBER, N. Studies of the metabolism of methadone (M) and methodology for isolation and quantification of the drug and its primary metabolite, 2-ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidine (P) using gas chromatography (GC) and mass spectrometry (MS). Federation Proceedings (in press)

For abstract, see Section I. Methodology of Drug Research.

McISAAC, W.M. Pharmacologic Studies on the Structure-Activity Relationship of Indolealkylamines. New York: Academic Press, 1969. Pp. 247-268.

McISAAC, W.M. Preliminary metabolism on 3H-STP in the rat and rabbit. Advances in Mental Science, Drug Dependence. Austin, Texas: University of Texas Press, 1972. Pp. 21-23.

McISAAC, W.M., HARRIS, R.T. and HO, B.T. Behavioral correlates of brain distribution of tetrahydrocannabinol. Acta Pharmaceutics Suecica 8: 671-706 (1971)

McMILLAN, D.E., DEWEY, W.L., TURK, R.F., HARRIS, L.S. and MCNEIL, J.H., JR. Blood levels of ^{3}H-delta-9-tetrahydrocannabinol and its metabolites in tolerant and nontolerant pigeons. Biochemical Pharmacology 22: 383-397 (1973)

Pigeons were made tolerant to the behavioral effects of l-delta-9-trans-tetrahydrocannabinol (delta-9-THC) by repeated intramuscular injections. The tolerant birds. as well as birds that had not received delta-9-THC previously, were injected with ^{3}H-delta-9-THC and blood samples were drawn over a period from 1 min to 2 weeks after injection. High levels of radioactivity appeared in the blood 1 min after injection and peak levels were reached in 30 min. after which there was a gradual decline with some radioactivity still present after 2 weeks. The levels of radioactivity in the petroleum ether-extractable fraction (mostly delta-9-THC by thin-layer chromatography (TLC)), in the diethyl ether-extractable fraction (mostly hydroxylated metabolites by TLC), and in the residue fraction of the plasma were also determined over the 2-week period. There were no differences between tolerant and nontolerant birds in levels of radioactivity in total plasma, or in any of the plasma fractions. In other experiments, seven injections of ^{3}H-delta-9-THC were given to pigeons over a 2-week period during which behavioral tolerance developed. Radioactivity gradually accumulated in the plasma of these birds: however, most of the radioactivity was accounted for in the residue fraction, with levels of radioactivity in the petroleum ether-extractable fraction and the diethyl ether-extractable fractions remaining at about the same levels after seven injections as after one injection. These results suggest that tolerant birds handle an injection of delta-9-THC in much the same manner as nontolerant birds, and that levels of delta-9-THC and its metabolites are as high as or higher in the blood of tolerant birds than they are in the blood of nontolerant birds. Thus, tolerance to delta-9-THC in the pigeon does not appear to be metabolic in origin.

McMONIGLE. J.J, and HORITA, A. Bioactivation of 5-oxo-(D-trans-2-phenylcycloprophyl)-L-2 pyrrolidone carboxamide(EX 4883) into monoamine oxidase inhibitor by a soluble fraction enzyme system. Archives internationales de Pharmacodynamie et de Therapie 178(1): 53-61 (March, 1969)

Numerous studies have emphasized that many drugs undergo biochemical transformation, and the resulting metabolites may be different chemically as well as producing different pharmacological actions. Included among these drugs are several monoamine oxidase (MAO) inhibitors, such as modaline (1,3) and furazolidone (6). The present paper describes another MAO inhibitor which appears to require biotransformation prior to its exerting anti-MAO activity. This was surmised when the compound 5-oxo-N-(D-trans-2-phenylcyclopropyl)-L-2-pyrrolidone carboxamide (EX 4883) was examined as a MAO inhibitor and found to be active in liver homogenates but not in isolated liver mitochondria. This study was undertaken to prove that EX 4883 is bioactivated prior to exerting its anti-MAO action, and to examine the characteristics of the bioactivating system.

MAICKEL. R.P., BRAUNSTEIN, M.C., McGLYNN, M., SNODGRASS, W.R. and WEBB, R.W. Behavioral, biochemical, and pharmacological effects of chronic dosage of phenothiazine tranquilizers in rats. The Phenothiazines and Structurally Related Drugs. Edited by I.S. Forrest, C.J. Carr and E. Usdin. New York: Raven Press, 1974.

For abstract, see Section I. Methodology of Drug Research.

MAICKEL, R.P., FEDYNSKYJ, N.M., POTTER, W.Z. and MANIAN, A.A. Tissue localization of 7- and 8-hydroxychlorpromazines. Toxicology and Applied Pharmacology 28: 8-17 (1974)

For abstract, see Section I. Methodology of Drug Research,

MAICKEL, R.P. and HARRISON, S.D., JR. Inability of rat brain homogenate to oxidize amphetamine. Biochemical Pharmacology 23:1146-1147 (1974)

MANDELL. A.J. Frontiers in the neurobiology of euphoria. American Handbook of Psychiatry, Vol. VI. Edited by S. Arieti, D.A. Hamburg and H.K. H. Brodie. New York: Basic Books, 1972.

For abstract, see Section I. Methodology of Drug Research.

MANDELL, A.J., editor. New Concepts in Neurotransmitter Regulation. New York: Plenum Press, 1973.

Proceedings of a conference on drug abuse and metabolic regulation of neurotransmitters, La Jolla, California, July, 1972.

MANDELL. A.J., SEGAL, D.S. and KUCZENSKI, R. Metabolic adaptation to anti-depressant drugs -- A neurochemical paradox. Catecholamines and Behavior. Edited by A. Friedhoff. New York: Plenum Press, 1974.

MANDELL, A.J., SEGAL. D.S. and Kuczenski. R. Metabolic adaptation to antidepressant drugs -- Implications for pathophysiology and treatment in psychiatry. Catecholamines and Behavior. Edited by A. Friedhoff. New York: Plenum Press, 1974.

MANNO, B.R. and MANNO. J.E. The marihuana dilemma: Has it been resolved? Toxicology Annual. Edited by C.L. Winek. New York: Marcel Dekker, Inc. (in press)

MANNO. J., MANNO. B., WALSWORTH, D. and HERD, R. Analysis and interpretation of the cannabinolic content of confiscated marihuana samples. Journal of Forensic Sciences 19(4): 844-890 (1974)

For abstract, see Section I. Methodology of Drug Research.

MARCH, J.E., DONATO, D., TURANO, P. and TURNER, W.J. Interpatient variation and significance of plasma levels of chlorpromazine in psychotic patients. Journal of Medicine 3:146-162 (1972)

Blood plasma from 50 chronic schizophrenics under long-term therapy with chlorpromazine was examined at 1.5 h after a morning dose and 12-15 h after an evening dose of medicine. The daily dose ranged from 150 to 3, 600 mg. Extractions were carried out with dichloromethane. The extracts were shaken with 2.5 ml H_2SO_4-Fe^{3+} color reagent, and the absorbance read at 530 nm. The limit of sensitivity using 20 ml of plasma was 0.15 mu-g/ml, at which level the plasma concentration of chlorpromazine and its metabolites in patients on 150 mg/day was measurable both at 1.5 and 12 h after medication. There was wide variation in plasma levels between individuals. As dose increased so did the levels at 1.5 and 12 h. Implications for clinical studies are discussed.

MARSHALL, I. and SMITH, C.B. The role of tyrosine hydroxylase in changes in brain catecholamine synthesis after acute and chronic administration of morphine to mice. Committee on the Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council, 1973. P. 351.

MARTIN, B.R., DEWEY, W.L. and HARRIS, L.S. Pharmacology of marihuana constituents. Virginia Journal of Science 25: 101 (1974)

Delta-8- and delta-9-tetrahydrocannabinol (THC), the active constituents of marihuana, are rapidly converted in vivo to their 11-hydroxy metabolites. It has been postulated that 11-hydroxylation of THC is a prerequisite to behavioral and pharmacological activity. We have accumulated evidence which indicates that delta-9-THC itself may be active. Thirty minutes after the intravenous injection of H^3-delta-9-THC (0.5 mg/kg) dogs were sacrificed, and the brains were removed, homogenized and extracted with petroleum ether and diethyl ether. Thin layer chromatography of these extracts revealed that 41% of the radio-activity was unchanged due to delta-9-THC. TLC of extracts from fetal dog brains showed that 60% of the radioactivity was unchanged delta-9-THC. The presence of high quantities of delta-9-THC and very low quantities of 11-hydroxy-delta-9-THC in dog brain at the time of peak activity do not support the hypothesis that only the 11-hydroxy metabolite is active. In addition, two analogs of delta-8-THC, 11-methyl- and 9-nor-delta-8-THC, were investigated for cannabinoid-like activity. 11-methyl-delta-8-THC is probably not converted to 11-hydroxy-delta-8-THC; whereas, 9-nor-delta-8-THC cannot be. In the unanesthetized dog, these analogs produce a cannabinoid-like effect on overt behavior. The intravenous minimal effective doses are 0.1-0.2 mg/kg for both delta-8-THC and delta-g-nor delta-8-THC, and 0.8-1.0 mg/kg for 11-methyl-delta-8-THC. In the anesthetized dog 9-nor-delta-8-THC is as effective as delta-8-THC in producing bradycardia and hypotension: whereas, 11-methyl-delta-8-THC is less effective.

MARTIN, B.R., DEWEY, W.L. and HARRIS, L.S. Subcellular distribution of 3H-delta-9-tetrahydrocannabinol in brains of nontolerant and tolerant rats. Proceedings of the Sixth International Congress of Pharmacology, Helsinki, Finland, July 20-25, 1975 (in press)

An i.p. injection of 10 mg/kg of delta-9-THC produced significant hypoactivity in rats. Tolerance to this effect was not observed following 6 but was seen after both 12 and 19 daily injections. The distribution of radioactivity one hour after the i.p. administration of 10 mg/kg of 3H-delta-9-THC was investigated in three groups of rats. One group had not been previously pretreated (naive), and the others had received either 6 or 19 daily injections of unlabeled delta-9-THC. There were no significant differences in plasma levels of radioactivity among the three groups. The radioactivity in the brains from naive rats was distributed among the following subcellular fractions: 25% in crude nuclear, 49% in crude mitochondria (CM), 8% in microsomes (MS), and 8% in supernatant (S). Cholinergic synaptosomes, noncholinergic synaptosomes, and synaptic vesicles were isolated from CM, and they contained 15%, 16%, and 12%, respectively, of the brain radioactivity, The brain subcellular distribution of radioactivity was similar for all three groups. The most notable exceptions were the MS and S fractions of the pretreatment groups which contained significantly more radioactivity than did those of the naive group. As tolerance developed, there was no reduction in the concentration of radioactivity in the synaptic vesicles. We have previously reported that the development of tolerance to delta-9-THC in dogs was associated with a significant decrease in the quantity of radioactivity found in the synaptic vesicle fraction.

MARTIN, B.R., DEWEY, W.L., HARRIS, L.S. and BECKNER, J. Marihuana-like activity of new synthetic tetrahydrocannabinols. Pharmacology Biochemistry and Behavior (in press)

The pharmacological profile and potency of 11-Methyl-delta-8, 9-nor-delta-8, and 9-nor-delta-9-tetrahydrocannabinol in laboratory animals was similar to that of delta-8- and delta-9-tetrahydrocannabinol. Each produced static-ataxia in unanesthetized dogs, bradycardia and hypotension in anesthetized dogs, and decreased spontaneous activity in mice. Two of these analogs cannot be converted to 11-hydroxy metabolites which indicates that 11-hydroxylation of delta-8- or delta-9-tetrahydrocannabinol may not be a prerequisite for biological activity of tetrahydrocannabinols.

MARTIN, B.R., DEWEY, W.L., HARRIS, L.S. and BECKNER, J.S. Subcellular localization of H^3-delta-9-tetrahydrocannabinol in dog brain after acute or chronic administration. The Pharmacologist 16(2): 395 (1974)

To ascertain if an alteration in the cellular or subcellular localization of delta-9-tetrahydrocannabinol (THC) in brain is responsible for tolerance, dogs received either one IV injection of 0.5 mg/kg of H^3-THC (70 mu-c/mg) or six daily IV injections of 0.5 mg/kg of THC followed by an injection of H^3-THC. Dogs were sacrificed 30 min. after the injection of H^3-THC, and their brains were removed for cellular and subcellular localization of H^3-THC. The pattern of distribution of radioactivity was similar for both groups of dogs. The greatest amount of radioactivity was in rostral and caudal colliculi, pituitary, hippocampus, thalamua, and geniculate bodies. Radioactivity in the gray matter of the cerebral cortex and cerebellum was 70.4 DPM/mg of tissue, whereas only 38.1 DPM/mg was found in the white matter. Also, the localization of radioactivity in the subcellular fractions was similar for both groups. The subcellular localization for the cerebral cortex was as follows: crude nuclear fraction (20%), crude mitochondrial (45%), microsomal (11%), and supernatant (15%). Thin layer chromatography of pet, ether and diethyl ether extracts of cerebral cortex showed that greater than 40% of the radioacitivy was unchanged THC.

MARTIN, B.R., HARRIS, L.S. and DEWEY, W.L. Behavioral and pharmacological properties of 11-methyl- and 9-nor-delta-8-tetrahydrocannabinol. Federation Proceedings 33: 540 (1974)

It has been demonstrated that delta-8-tetrahydrocannabinol (THC) is rapidly metabolized to 11-hydroxy-delta-8-THC in the body, and it has been postulated that this metabolite is responsible for the activity of delta-8-THC. We have investigated the pharmacological properties of two analogs of delta-8-THC, 11-methyl- and 9-nor-delta-8-THC. The former is probably not converted to an 11-hydroxy metabolite, the latter cannot be. In the unanesthetized dog these analogs produce prance-like placement of feet, static ataxia, hyperreflexia and a decrease in spontaneous activity. This profile of behavior is the same as that seen after delta-8- or delta-9-THC. The intravenous minimal effective doses are 0.2-0. 4 mg/kg for both delta-8-THC and 9-nor-delta-8-THC and 0.8-1.0 mg/kg for 11-methyl-delta-8-THC. In the anesthetized dog 9-nor-delta-8-THC is again as effective as delta-8-THC in producing bradycardia and hypotension: as before, 11-methyl-delta-8-THC is somewhat less effective. In mice delta-8-THC, 9-nor-delta-8-THC, and 11-methyl-delta-8-THC have no effect on hexobarbital-induced sleeping time and exhibit no antinociceptive activity as measured in the tall flick or hot plate test. Each compound has some activity in the phenylquinone writhing test, delta-8-THC being more active than either analog.

MECHOULAM. R. Cannabinoid chemistry. Marijuana. Chemistry, Metabolism, Pharmacology and Clinical Effects. Edited by R. Mechoulam. New York: Academic Press, 1973. Pp. 1-88.

MECHOULAM, R. Chemistry and cannabis activity. Ciencia e Cultura 25(8): 742 (1973)

MECHOULAM, R. Marihuana chemistry. Review. Science 168: 1159 (1970)

MECHOULAM, R., BEN-ZVI, Z., AGURELL, S., NILSSON, I.M., NILSSON. J.L.G. EDERY, H. and GRUNFELD. Y. Delta-6-tetrahydrocannabinol-7-oic acid, a urinary delta-6-THC metabolite: Isolation and synthesis. Experientia 29: 1193 (1973)

MECHOULAM, R., BEN-ZVI, Z. and GAONI, Y. Hashish XIII.On the nature of the Beam test. Tetrahedron Letters 24: 5615 (1968)

The purple colour produced by treatment of cannabidiol (1) with 5% ethanolic potassium hydroxide (Beam test) is due to the anions of the hydroxy-quinone II and its dimer III. Compounds II and III are formed from I by air oxidation during the reaction. The diquinone III is reduced in the mass spectrometer to a $M^+ + 4$ species (probably the dihydroquinone).

MECHOULAM, R., BEN-ZVI, Z., SHANI, A., ZEMLER, H., LEVY, S., EDERY, H. and GRUNFELD. Y. Cannabinoids and cannabis activity. Cannabis and Its Derivatives. Pharmacology and Experimental Psychology. Edited by W.D.M. Paton and J. Crown. Fairlawn, New Jersey: Oxford University Press, 1972.

MECHOULAM. R., BEN-ZVI, Z., VARCONI, H. and SAMUELOV, Y. Cannabinoid rearrangements. Synthesis of delta-5-tetrahydrocannabinol. Tetrahedron Letters 29: 1615-1619 (1973)

1-beta, 6-beta-Epoxy-hexahydrocannabinol acetate (1) in the presence of borontrifluoride rearranged to 6-oxo-hexahydrocannabinol acetate and to the aldehyde. Hydroboration of delta-6-THC gave the 6-hydroxy hexahydrocannabinols and 8a. The latter was converted into delta-5-THC. This THC isomer shows no cannabis-type activity in rhesus monkeys.

MECHOULAM, R., BEN-ZVI, Z., YAGNITINSKY. B. and SHANI, A. A new tetrahydrocannabinolic acid. Tetrahedron Letters 28: 2339 (1969)

MECHOULAM, R., BRAUN, P. and GAONI, Y. Hashish XI. A stereospecific synthesis of (-)-delta-1- and (-)-delta-1$^{(6)}$-tetrahydrocannabinol. Journal of the American Chemical Society 89: 4551 (1967)

MECHOULAM, R., BRAUN, P. and GAONI, Y. Syntheses of delta-1-tetrahydrocannabinol and related cannabinoids. Journal of the American Chemical Society 94: 6159 (1972)

Addition of citral to the lithium derivative of olivetol dimethyl ether, followed by reaction with p-toluenesulfonyl chloride, gave (±)-cannabidiol dimethyl ether. Demethylation afforded (±)-cannabidiol, which was converted into (±)-delta-1-tetrahydrocannabinol (delta-1-THC) in a low overall yield. An improved synthesis of (±)-delta-1-THC was achieved by the reaction of citral with olivetol in the presence of 1% boron tri-fluoride etherate. Reaction of (+)- or (–)-verbenol with olivetol under the same conditions gives (+)- or (–)- delta-6-THC, respectively. This reaction can be further improved (to 48%) by a stepwise synthesis through the intermediate 4 trans-(2-olivetyl) pinene. Addition of hydrogen chloride to the double bond of (+)-or (–)-delta-6-THC, followed by dehydrochlorination, leads to (+)- or (–)-delta-1-THC. A method for the preparation of (3-^{2}H)-delta-1-THC is described.

MECHOULAM, R. and EDERY. H. Structure-activity relationships in cannabinoid series. Marijuana. Chemistry, Metabolism, Pharmacology and Clinical Effects. Edited by R. Mechoulam. New York: Academic Press, 1973. Pp. 101-133.

MECHOULAM, R. and GAONI, Y. Hashish X. The absolute configuration of delta-1-tetrahydrocannabinol, the major active constituent of hashish. Tetrahedron Letters 12: 1109-1111 (1967)

MECHOULAM, R. and GAONI. Y. Recent advances in the chemistry of hashish. Review article. Progress in the Chemistry of Organic Natural Products. (Fortschritte der Chemie Organischer Naturstoffe). Edited by L. Zechmeister. New York: Springer-Verlach-Verlag, 1967.

MECHOULAM, R., SHANI, A., YAGNITINSKY, B., BEN-ZVI, Z., BRAUN. P. and GAONI, Y. Some aspects of cannabinoid chemistry. Botany and Chemistry of Cannabis. Edited by C.R.B. Joyce and S.H. Curry. London, England: 7. and A. Churchill, 1970. Pp. 93-117.

MECHOULAM, R., VARCONI. H., BEN-ZVI, Z., EDERY, H. and GRUNFELD, Y. Synthesis and biological activity of five tetrahydrocannabinol metabolites. Journal of the American Chemical Society 94: 7930 (1972)

MECHOULAM, R. and YAGEN. B. Stereoselective cyclizations of cannabinoid 1,5 dienes. Tetrahedron Letters 60: 5349 (1969)

MECHOULAM, R., YAGNITINSKY, B. and GAONI, Y. Hashish XII. Stereoelectronic factor in the chloranil dehydrogenation of cannabinoids. Total synthesis of dl-cannabichromene. Journal of the American Chemical Society 90: 2418 (1968)

MEDZIHRADSKY, F., MARKS, M.J. and CARR, E.A., JR. Energy-dependent uptake of benzomorphans by leukocytes. Biochemical Pharmacology 21: 1625-1632 (1972)

Pentazocine rapidly enters the brain after i.p. administration to rats. Using leukocytes as model mammalian cells, the uptake of this drug was studied, Morphologically intact and metabolically active rat leukocytes accumulated pentazocine in vitro against a concentration gradient. The 6- to 10-fold concentration of the drug was dependent upon the presence of glucose in the incubation medium and was strongly affected by metabolic inhibitors present in millimolar concentrations. The uptake showed saturation kinetics in the concentration range of 1.7-14 X 10^{-5} M pentazocine and was competitively inhibited by analogue benzomorphan derivatives. Ouabain as well as sodium-free extracellular media had no effect on the uptake of pentazocine. The transport system for pentazocine in the leukocyte apparently differs from the relatively nonspecific amine pump which accumulates various organic bases in the blood platelet.

MEDZIHRADSKY. F., MARKS, M.J. and METCALF, J.I. Cellular transport of CNS drugs in leukocytes. Biochemical Advances in Psychopharmacology (in press)

MEDZIHRADSKY. F. and NANDHASRI. P.J. Effects of some analgesics and antidepressants on the (Na^+ + K^+)--adenosine triphosphatase from cortices of brain and kidney. Biochemical Pharmacology 21: 2103-2109 (1972)

The effects of benzomorphans, tricyclic antidepressants, monoamine oxidase (MAO) inhibitors and chlorpromazine on the microsomal (Na^+ + K^+)-adenosine triphosphatase (ATPase) from beef cerebral cortex were studied. As a comparison, the interaction of these drugs with the corresponding enzyme from kidney cortex as also investigated. In addition to chlorpromazine, the benzomorphans and the tricyclic antidepressants inhibited the brain enzyme considerably, whereas the MAO inhibitors had little effect. The (Na^+ + K^+)-ATPase from kidney was not affected by the benzomorphans or MAO inhibitors, but its activity diminished in the presence of the tricyclic antidepressants and chlorpromazine.

MELIKIAN, A.P. and FORREST, I.S. Dansyl derivatives of delta-9- and delta-8-tetrahydrocannabinols. Journal of Pharmaceutical Sciences 61: 1025-1026 (1973)

MELIKIAN, A.P., GREEN. D.E., SKINNER, J.L. and FORREST, I.S. Isolation of in vivo delta-9-tetrahydrocannabinol metabolites from primate urine. Proceedings of the Western Pharmacological Society 16: 234-239 (1973)

MEYERHOFF, J.L. and SNYDER, S.H. Gilles de la Tourette's Disease and minimal brain dysfunction: Amphetamine isomers reveal catecholamine correlates in an affected patient. Psychopharmalogia 29: 211-220 (1973)

Graduated doses of d- and l-isomers of amphetamine were administered on several occasions in double blind fashion to a patient with' symptoms of both Gilles de la Tourettes disease and minimal brain dysfunction. d-Amphetamine markedly increased the frequency of ticking while l-amphetamine did not alter the tics. By contrast both isomers decreased the patient's hyperactivity to a similar extent. Based on the known differential influence of amphetamine isomers upon brain norepinephrine and dopamine, these findings suggest that aggravation of the tics is mediated by brain norepinephrine, while brain dopamine plays a major role in the alleviation of the symptons of minimal brain dysfunction.

MILLER, R.J., JOLLES, C. and RAPOPORT. H. Morphine metabolism and normorphine in papaver somniferum. Phytochemistry 12: 597 (1973)

MISRA, A.L., BLOCH, R., VADLAMANI, N.L. and MULE, S.J. Physiological disposition and biotransformation of levo-methadone-1-^{3}H in the dog. The Journal of Pharmacology and Experimental Therapeutics 188(1): 34-44 (1974)

A method with minimal sensitivity of 1 to 2 ng, previously developed for levo-methadone after small doses has been used to estimate this drug in selected anatomical areas of the central nervous system and the peripheral tissues of the dog. After a 2 mg/kg (free base) s.c. dose of levo-methadone-1-^{3}H to the dog, peak levels of drug in plasma (143 ng/ml) and in different anatomical areas of the central nervous system (1270-2029 ng/g) occurred at two hours. Measurable quantities of drug persisted in different areas of the dog brain and peripheral tissues for at least three weeks. At the same time the concentrations in plasma were barely detectable at periods of one and three weeks after drug administration. High levels of methadone were observed in lung, liver, spleen, kidney, heart and intestine with somewhat lower concentrations in muscle and fat. The approximate half-life of levo-methadone in dog plasma after a 2 mg/kg s.c. dose was six to seven hours and that in temporal cortex, hypothalamus, cerebellum and caudate nucleus ranged between three and four hours. The mean percentages of free drug excreted in the urine and feces of dogs 96 hours after a single 2 mg/kg s. c. dose were 19.4%. conjugated acid-hydrolyzable metabolites, 5.4% and total radioactivity, 68.3%. The values of conjugated metabolites and total radioactivity in dogs given chronic injections of methadone were significantly lower than those in acute animals. levo-Methadone was extensively metabolized by: 1) N-dealkylation and cyclization to substituted pyrrolidine and pyrroline metabolites; 2) N-oxidation; 3) hydroxylation in the para position of the aromatic nucleus; 4) keto group reduction; 5) glucuronide conjugation of resultant hydroxyl groups; and 6) minor conversion of secondary and primary amines. Persistence of levo-methadone and a metabolite in selected anatomical areas of the central nervous system of the dog and the binding of the metabolite to a specific brain protein could conceivably lead to a biochemical alteration of the receptor site and result in a reduced ability of the drug to initiate a pharmacological response. Possible relevance of these observations to the phenomena of pharmacological tolerance and the protracted course of the withdrawal syndrome observed with methadone are described.

MISRA. A.L. and MITCHELL, C.L. Determination of morphine-N-methyl-C^{14}oxide in biological materials, its excretion and metabolites in the rat. Biochemical Medicine 5: 379-383 (1971)

A method for determination of morphine -N-methyl-^{14}C oxide in biological materials has been described which gave approximate recoveries of N-oxide as 94, 82, and 77% from urine or plasma, liver and brain tissue, respectively. On subcutaneous injection of 20 mg/kg of morphine N-methyl-^{14}C-oxide, male Sprague-Dawley rats excreted 80.6-91.5% of total radioactivity in urine and feces, 19.6-41.2% as free N-oxide, 6.2-24.3% as free morphine and 3.6-6.9% as morphine-3-glucuronide. Column and thin-layer chromatography established morphine, morphine-3-glucuronide, and normorphine (5-10%) as principal urinary metabolites of morphine N-oxide in the rat. Evidence for the formation of N-oxide as a metabolite of morphine in the central nervous system of rats was not obtained. Morphine N-oxide can be converted nonenzymatically to morphine and normorphine by ferrous iron and cysteine.

MISRA, A.L. and MITCHELL, C.L. Metal ion-catalyzed interaction of peroxidase with morphine and protein. Experientia 27: 1442-1444 (1971)

MISRA, A.L., MITCHELL, C.L. and WOODS, L.A. Persistence of morphine in the central nervous system after a single injection and its bearing on tolerance. Nature 232: 48-50 (1971)

MISRA, A.L. and MULE, S.J. Persistence of methadone-^{3}H and metabolite in rat brain after a single injection and its implications on pharmacological tolerance. Nature 138: 155-156 (July, 1972)

MISRA, A.L. and MULE, S.J. Stereoselectivity and differential metabolism in vivo of dextro and laevo-methadone-1-^{3}H. Nature 241: 281-283 (January, 1973)

MISRA, A.L., MULE. S.J., BLOCH, R. and VADLAMANI, N. L. Physiological disposition and metabolism of Levo-methadone-1-^{3}H in nontolerant and tolerant rats. The Journal of Pharmacology and Experimental Therapeutics 185(2):287-299 (1973)

A method is described for the estimation of levo-methadone-1-^{3}H in biological materials which has a minimal sensitivity of 1 to 2 ng. After a dose of levo-methadone-1-^{3}H 10 mg kg s.c., to male Wistar rats, the mean peak levels were 1798 ng/ml in plasma at 0.5 hour and 4502 ng/g in brain at 1 hour, respectively. Measurable quantities of drug persisted in brain (20 ng/g)) and other tissues up to three weeks or longer, even though no measurable amounts of drug were present in plasma after 24 hours. Orally administered drug (10 mg/kg) produced levels in plasma and brain approximately 1/25 of those observed after subcutaneous injection. The drug was localized in lung, liver, kidney and brain, with lower concentrations in heart and muscle. The mean percentages of free drug excreted in 96-hour urine and feces after injection of 10 mg/kg s.c. were 11.37 and 14.78, respectively. The total radioactivity values in urine and feces were 19.49% and 29.8%, respectively. After an injection of 10 mg/kg s.c., the concentrations of drug in brain and plasma of tolerant rats were consistently lower than those in nontolerant rats at each time interval. After oral administration of methadone (50 mg/kg), the concentrations at 0.5 and 1 hour in brain and plasma of tolerant rats were higher and subsequently dropped to values lower than those observed in the nontolerant rats. The approximate half-lives of drug in brain and plasma of nontolerant rats after 10 mg/kg s.c. injections were 2. 4 and 3. 7 hours, respectively, and in tolerant rats 1.5 and 1.7 hours, respectively. By the oral route (50 mg/kg), half-lives in brain and plasma of nontolerant rats were approximately 14 and greater than 8 hours respectively, and in tolerant rats, 3.1 hours in brain and 1.4 hours in plasma. The rate of disappearance of drug from plasma and brain was faster in the tolerant rats and there was evidence for a faster rate of metabolism of drug in these animals. The drug was extensively metabolized and in addition to known substituted pyrrolidine, pyrroline and N-oxide metabolites, evidence of six other phenolic glucuronide-conjugated amines was obtained. Four had the characteristics of a phenolic teritary amine, one a secondary amine and the other a primary amine, respectively. Evidence for the presence of a phenolic primary methadone metabolite with structural similarity to norepinephrine was obtained in rat brains at the time of peak analgesia. Later, this metabolite conjugated with protein persisted in brain along with free methadone. These observations, coupled with consistent differences in physiological disposition of methadone in brain and plasma of nontolerant and tolerant rats. may have relevance to the mechanism of pharmacological tolerance and the protracted withdrawal syndrome observed with methadone.

MISRA, A.L., VADLAMANI, N.L., MULE, S.J. Chromatographic separation of methadone, some of its metabolites and congeners. Journal of Chromatography 67: 379-381 (1972)

MOLE, M.L., JR. and TURNER, C.E. Phytochemical screening of Cannabis sativa L. H. Choline and neurine in the roots of a Mexican variant. Acta Pharmaceutica Jugoslavica 23(4): 203-205 (1973)

For abstract, see Section I. Methodology of Drug Research.

MULE S.J., CASELLA, G. and CLOUET, D.H. The localization of levo-H^3-methadone in isolated synaptic membranes of rat brain. Committee on Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council, 1972.

It certainly appears from these studies that a degree of specificity is associated with localization of ^{3}H-methadone in the mu 1 (1.0) synaptic membrane fraction of brain. The extent of this specificity especially in relation to the narcotic receptor is now under investigation.

MULE. S.J. and CLOUET, D.H. Pharmacological and biochemical aspects of opiate dependence. Psychopharmacologia 26: 116 (1972)

The chronic use of narcotic analgesic drugs induces a drug-dependent state that has distinguishing characteristics which are quite different from the characteristics of the dependence induced by the use of other classes of drugs. In order to define the opiate-dependent state, objective criteria which characterize physiological and psychological dependence will be described. The chemical aspects of narcotic drug action will be considered including localization of opiates in subcellular sites in the brain, the possible relation of this localization to the opiate receptor, biotransformation of drugs, and its correlation with pharmacological action. With this background the theories associated with the development of tolerance, physical and psychic dependence, such as pharmacological denervation supersensitivity, pharmacological redundancy, silent and active receptors, depression and repression of enzymes, macromolecular biosynthesis, and the role of neurotransmitters with special emphasis upon norepinephrine, acetylcholine, dopamine and serotonin will be discussed, as will the role of physical dependence in the perpetuation of drug-seeking behavior and its relationship to relapse.

MULE. S.J. and MISRA, A.L. Disposition and metabolism of levo-methadone-1-methyl-^{3}H in the rat. Federation Proceedings 31: 528 (1972)

NIELSEN, M., EPLOV, L. and SCHEEL-KRÜGER. J. The effect of amitriptyline. desipramine and imipramine on the in vivo brain synthesis of ^{3}H-L-dopa in the rat. Psychopharmacologia (in press)

NIELSEN, M. The effects of amitriptyline, desipramine, imipramine and protriptyline on the in vivo brain synthesis of 3H-noradrenaline from 3H-1-dopa in the rat. Acta Pharmacologica et Toxicologica 35(Supplement I): 43 (1974)

In rats 3H-L-DOPA was given after a peripheral decarboxylase inhibitor Ro 4-4602 (50 mg/kg) and the effect of 30 min pretreatment with amitriptyline (10 mg/kg), desipramine (10 mg/kg), imipramine (10 mg/kg) or protriptyline (10 mg/kg) on the brain formation of 3H-dopamine (3H-DA), 3H-noradrenaline (3H-NA) and their major metabolites was investigated. Protriptyline, desipramine and imipramine produced a decrease in the brain level of labelled noradrenaline and its metabolites 3-methoxy-4-hydroxyphenylglycol and 3,4-dihydroxyphenylglycol 60 min after 3H-L-DOPA. These findings thus strongly indicate that protriptyline, desipramine and imipramine inhibit 3H-NA synthesis from 3H-L-DOPA. Amitriptyline produced no effect on 3H-NA metabolism.

The accumulation of labelled dopamine and its metabolites was increased by amitriptyline, while the other thymoleptics showed only tendencie to increase 3H-DA accumulation and metabolism. The thymoleptic drugs produced no significant effect on endogenous brain noradrenaline and dopamine.

Experiments on the effect of tricyclic antidepressant drugs on central 3H-NA metabolism with the use of 3H-L-Tyrosine, 3H-DA or 3H-NA as labelled precursors are in progress.

NILSSON, I.M., AGURELL, S., NILSSON, J.L.G., OHLSSON, A., LINDGREN. J.E. and MECHOULAM, R. Metabolism of 7-hydroxy-delta-1(6)-tetrahydrocannabinol in the rabbit. Acta Pharmaceutica Suecica 10:97 (1973)

The distribution, conversion and elimination of 7-hydroxy-delta-1(6)-THC-^{3}H has been studied in the rabbit. The compound was quickly distributed from the blood after i.v. injection and rapidly converted to metabolites. After 10 min. less than half of the radioactivity in blood was due to the originally administered compound.

NILSSON, J.L.G., NILSSON, I.M., AGURELL. S., BEN-ZVI, Z. and MECHOULAM, R. Synthesis of a potential urinary THC metabolite. Acta Pharmaceutica Suecica 9:215 (1972)

7-Hydroxy-delta-1, 6-THC was methylated on the phenolic hydroxyl groups whereupon the hydroxymethyl group was oxidized, using chromic acid or MnO_2 to the corresponding crystalline aldehyde 7. This was further oxidized to the corresponding carboxylic acid methyl ester 8 using MnO_2 and NaCN in methanol. When the ester 8 was compared chromatographically with the methylated acidic metabolites of delta-1-THC, the metabolite(s) turned out to be more polar than the synthetic compound, indicating that the metabolite(s) appear to have more polar groups than the synthetic molecule.

PAL, B.K., GOLDSTEIN, A. and LOWNEY, L. Stereospecific binding of the morphine congener levorphanol by mouse brain preparations. Federation Proceedings 30: 272 (1971)

Since the pharmacological effects of opiates are highly stereospecific (only D(-) isomers are active), the present investigation was undertaken to study the stereospecific binding (SSB) of levorphanol by mouse brain preparations. SSB is measured as the difference in binding of radioactive levorphanol under two conditions: (1) in the presence of a large excess of nonradioactive dextrorphan, the L(+) isomer, and (2) in the presence of a large excess of nonradioactive levorphanol.

Our results show that among the different subcellular fractions of mouse brain, only one fraction has the SSB capacity. This material initially sediments with crude nuclei but subsequently floats on 2 M sucrose when the crude nuclear preparation is centrifuged through this medium. The SSB capacity of this membrane preparation is not extractable either by 0.5% triton-X 100 or by 0.1% sodium lauryl sulfate in cold, although 70% of the protein is solubilized by either of these treatments. The SSB is pH dependent, the optimum pH being in the range of 7.2 to 7.4. The SSB is inhibited by Ca^{2+} and Mg^{2+}. although the same concentration of Na^{+} has no effect. The SSB is stimulated by ethylenediamine tetraacetate. Iodo-acetic acid, p-chloromercuribenzoate and beta-mercaptoethanol have no significant effect on SSB.

PASTERNAK, G.W. and SNYDER, S.H. Identification of novel high affinity opiate receptor binding in rat brain. Nature (in press)

PASTERNAK, G.W. and SNYDER, S.H. Opiate receptor binding: Effects of enzymatic treatments. Molecular Pharmacology 10: 183-193 (1974)

A variety of enzymatic treatments have been examined with regard to their effect on stereospecific (^{3}H) naloxone binding to rat brain homogenates. Opiate receptor binding is sensitive to very low concentrations of trypsin (EC 3.4.4.4) and chymotrypsin (EC 3.4.4.5). Trypsin appears to decrease the number of opiate receptor binding sites. while chymotrypsin primarily lowers their affinity for opiates. Receptor binding is drastically reduced by very low concentrations of phospholipase A (EC 3.1.1.4), is decreased by higher concentrations of phospholipase C (EC 3.1.4.3), and appears relatively insensitive to phospholipase D (EC 3.1.4.4) and neuraminidase (EC 3.2.1.18). Small amounts of RNase (EC 2.7.7.16) and DNase (EC 3.1.4.5) are without effect. Trypsin and chymotrypsin decrease receptor binding in a biphasic fashion, suggesting the presence of more than one population of sites sensitive to protcolysis. By contrast, the phospholipases degrade binding in a monophasic fashion. Thus the opiate receptor appears to be a membrane-bound complex whose stereospecific binding is dependent upon the integrity of both proteins and phospholipids.

PASTERNAK, G.W., WILSON, H.A. and SNYDER, S.H. Differential effects of protein modifying reagents on receptor binding of opiate agonists and antagonists. Molecular Pharmacology (in press)

PATRICK, G.A., DEWEY, W.L., HARRIS, L.S., DAVES, E.D. and NEUMANN, J.H. Relationship of brain morphine concentration to tail-flick activity and tolerance and dependence development in chronically infused rats. The Pharmacologist 16(2): 71 (1974)

Rats were treated chronically with morphine (M) sulfate by the i.p. infusion technique of Teiger. Brain M concentration was measured throughout the infusion and withdrawal periods by a fluorometric technique similar to that of Kupferberg et al. The onset of analgesia was within 60 minutes of the beginning of infusion, and brain M levels were measurable at that time. The rate and degree of tolerance development was dependent upon the infusion schedule employed. Some tolerance was observed after 24-48 hours of infusion, but tolerance was greatest only after 48 hours or more of infusion at a rate of 200 mg M sulfate/kg/day. Tolerance appeared to be both cellular and metabolic in nature, since tail-flick response decreased while brain M was elevated, and brain M level began to decline as the infusion period was lengthened. Upon cessation of the infusion, brain M levels declined precipitously within 6 hours, but tolerance to the analgesic effect of M was evident for a longer period. Loss of body weight was maximal (20-25%) at 24 hours after the infusion was stopped; however, this sign of dependence was not observed if a pellet of naloxone was implanted at the beginning of the infusion regimen.

PAUL, A.G., KHANNA, K.L., ROSENBERG, H. and TAKIDO, M. Biosynthesis of peyote alkaloids. Chemical Communications, 1969. London, England: The Chemical Society, 1969. P. 838.

A pathway of biosynthesis of mescaline and the phenolic tetrahydroisoquinoline alkaloids of peyote is suggested.

PAUL, A.G., ROSENBERG, H. and KHANNA, K.L. The roles of 3,4,5-trihydroxy-beta-phenethylamine and 3,4-dimethoxy-beta-phenethylamine in the biosynthesis of mescaline. Lloydia 32(1): 36-39 (March, 1969)

Following the injection of 8-^{14}C-normescaline and 8-^{14}C-3,4-dimethoxy-beta-phenethylamine into plants of L. williamsii, radioactive mescaline was isolated, characterized, assayed for specific activity, and degraded. The data indicate that both of these compounds serve as precursors of mescaline. However, the low percentage of incorporation of normescaline suggests that it is not a direct precursor. The relatively high percentage of incorporation of 3,4-dimethoxy-beta-phenethylamine strongly supports the hypothesis that this compound is a direct precursor of mescaline, arising from dopamine by O-methylation.

PAUL, S.M., HSU, L,L. and MANDELL, A.J. Extrapineal N-acetyltransferase activity in rat brain. Life Sciences 15(12): 2135-2143 (1973)

For abstract, see Section I. Methodology of Drug Research.

PERT, C.B., PASTERNAK, G. and SNYDER, S.H. Opiate agonists and antagonists discriminated by receptor binding in brain. Science 182: 1359-1361 (December, 1973)

Receptor binding of opiate agonists and antagonists can be differentiated in vivo and in vitro. Administration of either rapidly elevates stereospecific (^{3}H) dihydromorphine binding to mouse brain extracts by 40 to 100 percent, but antagonists are 10 to 1000 times more potent than agonists; as little as 0.02 milligram of naloxone per kilogram of body weight significantly enhances opiate receptor binding. Sodium enhances antagonist binding in vitro but decreases agonist binding, a qualitative difference that may be relevant to the divergent pharmacological properties of opiate agonists and antagonists.

PERT, C.B. and SNYDER, S.H. Opiate receptor binding: Enhancement by in vivo opiate administration. Biochemical Pharmacology (in press)

PERT, C.B. and SNYDER, S.H. Opiate receptor binding of agonists and antagonists affected differentially by sodium. Molecular Pharmacology 10: 868-879 (1974)

Receptor binding of the tritiated opiate antagonists naloxone, nalorphine, and levallorphan is enhanced by sodium ion. while binding of the tritiated agonists oxymorphone, dihydromorphine, and levorphanol is diminished. This differential effect of Na^+ is highly specific, since it is elicited by Na+ and Li^+ but not by other monovalent or divalent cations. The relative effectiveness of nonradioactive opiates in inhibiting (^{3}H) naloxone binding in the absence and presence of Na+ in vitro correlates impressively with their relative agonist-antagonist properties in vivo. It is hypothesized that sodium allosterically transforms opiate receptor sites from conformations which bind agonists more readily to conformations which bind antagonists more readily. This hypothesis is supported by the competition of opiate agonists and antagonists for receptor sites, the marked temperature dependence of binding, the similar extent of binding of tritiated agonists and antagonists at maximal saturation, the concurrent increruse in naloxone binding Bites and decrease in dihydromorphine binding Bites caused by the addition of Na^+, and the ability of Na^+ to increase (^{3}H) dihydromorphine dissociation with no effect on (^{3}H) naloxone dissociation.

PERT, C.B. and SNYDER, S.H. Opiate receptor: Demonstration in nervous tissue. Science 179: 1011-1014 (March, 1973)

Tritiated naloxone, a powerful opiate antagonist, specifically binds to an opiate receptor of mammalian brain and guinea pig intestine. Competition for the opiate receptor by various opiates and their antagonists closely parallels their pharmacological potency. The opiate receptor is confined to nervous tissue.

PERT, C.B. and SNYDER, S.H. Properties of opiate-receptor binding in rat brain. Proceedings of the National Academy of Sciences 70(8): 2243-2247 (August, 1973)

Naloxone, a potent opiate antagonist, binds stereoespecifically to opiate-receptor sites in rat-brain tissue. The binding is time, temperature, and pH dependent and saturable with respect to /^{3}H/ naloxone and tissue concentration. The /^{3}H/ naloxone-receptor complex formation is bimolecular with a dissociation constant of 20nM. 15 Opiate agonists and antagonists compete for the same receptors, whose density is 30 pmol/g. Potencies of opiates and their antagonists in displacing /^{3}H/ naloxone binding parallel their pharmacological potencies.

PETERS, M. A. The effect of acute and chronic methadone treatment on the in vitro n-demethylation of methadone by microsomal enzymes of male and pregnant and nonpregnant female rats. Archives internationales de Pharmacodynamie et de Therapie 205(2): 259-266 (October, 1973)

Male rats were found to metabolize (N-demethylate) methadone about twice as fast as female rats. Acute treatment tended, to increase the rate of metabolism in male rats but not in female rats, while chronic treatment had little effect in either sex. Pregnancy tended to decrease the rate of metabolism, however, the only significant difference between pregnant and nonpregnant female rats was seen in the chronically treated group. Increaeing certain cofactor concentrations caused a greater increase in the rate of metabolism in male rats than in female rats. Microsomes from fetal livers of all treatment groups were totally devoid of metabolic activity. The kinetic studies would suggest that the decrease in metabolism caused by pregnancy is a competitive type inhibition, while the increased metabolism seen in the male appears to be both qualitatively and quantitatively different from the female since both the K_m and V_{max} were significantly different.

PILLARD, R.C. Medical progress. Marihuana. New England Journal.of Medicine 283:294-303 (August, 1970)

PLAIN, W. M., CAUTHEN, S. E. and KIDD, M. R. Human Berum tropacocainesterase. Presented at the American Chemical Society 30th Southwest Regional Meeting, Houston, Texas, December 9-11, 1974.

An enzyme which catalyzes the hydrolysis of tropacocaine has been partially purified from pooled human serum using ammonium sulfate fractionation, DEAE-Sephadex ion exchange chromatography and gel filtration. Reports in the literature conflict with respect to whether this enzyme is identical to pseudocholinesterase, acylcholine acyl-hydrolase (E.C. 3.1.1.8). Attempts have been made to resolve this conflict on the basis of substrate specificity and inhibition studies. Samples of individual human sera were examined using analytical scale polyacrylamide gel electrophoresis in attempts to determine the distribution of tropacocainesterase.

POLLOCK, S.H. and FUJIMOTO, J.M. A partial characterization of naloxone and naltrexone-6-ketone reductases in rabbit and chicken. The Pharmacologist 16: 225 (1974)

The stereospecific identification of the reduction products of the narcotic antagoniets (naloxone and naltrexone) by N. Chatterjie et al. (this meeting) goes hand in hand with this work in which the enzyme systems are partially characterized. Both the hepatic enzyme from the rabbit and the chicken which respectively produce the 6-beta-OH and 6-alpha-OH reduction products are NADPH dependent enzymes occurring in the soluble cell fractions. The enzyme assay conlisted of purified enzyme protein mixture; 7.9 mu-mol glucose-6-phosphate; 0.25 mu-mol NADP; and 2 units glucose-6-phosphate dehydrogenase in a final volunie of 1 ml 0.05 M KH2P04/NaOH buffer (pH 7.4) with N-allyl-1, 3-^{14}C naloxone or ^{3}H-15, 16-naltrexone. The Km's of both naloxone and naltrexone are similar (ca. 10-^{4}M) for both enzymes. The shapes of the pH-activity curves are similar. The rabbit enzyme is inhibited more by 6-alpha-OH dihydromorphine derivatives than the chicken enzyme. These enzymes do not appear to be involved in reduction of certain other ketones. The rabbit liver enzyme is a better model than the chicken for the human metabolic pathway of naltrexone reduction since in man and the rabbit the reduced product has the 6-beta-OH configuration.

RANDRUP; A. and MUNKVAD, I. Mechanisms by which amphetamines produce stereotypy, agression [sic] and other behavidural effects. Psychopharmacologia 26 (supplement): 37 (1972)

The dopaminergic systems in the forebrain (nucleus caudatus, putamen and some adjacent areas) appear to have effects, in mammals, on many perhaps all types of behaviour, and these effects tend in the extreme to change the whole pattern of behaviour into a stereotyped, apparently aimless one. At the same time each type of behaviour e.g. locomotion, aggressive and other social activities, drinking etc. appear to be influenced also by other brain systems. The behavioural effects of a drug, which like amphetamines acts on several brain systems (dopaminergic, noradrenergic, serotonergic and possibly others) are therefore bound to be complicated. For example: smaller doses of d-amphetamine cause increase in locomotion of rats while larger doses cause inhibition. The increased locomotion can be stereotyped, consisting in repetition of a fixed route in a restricted part of the cage. Brain dopamine plays a role in these locomotor effects, but locomotion is also influenced by brain noradrenaline. Recent findings about the mechanisms by which amphetamines produce their behavioural effects will be reviewed. Real and apparent contradictions in the most recent publications about experiments with brain lesions will be discussed; the extent of lesions in the striatum and the slow recovery of behaviour after such lesions seem to be important items in this context.

RAZDAN, R.K., DALZELL, H.C. and HANDRICK, G.R. Hashish. A simple one-step synthesis of (-)-delta-1-tetrahydrocannabinol (THC) from p-mentha-2, 8-dien-1-ol and olivetol. Journal of the American Chemical Society 96(18): 5860-5865 (September, 1974)

Optically pure (-)-delta-1-THC was produced in 50% yield (glc; isolated yield 31%) in a single-step synthesis from cis/trans-(+)-p-mentha-2, 8-dien-1-ol and olivetol in the presence of 1% boron trifluoride etherate and anhydrous mxnesium sulfate in methylene chloride at 0°. The product was readily separated by column chromatography. The other major product formed was trans-delta-8-iso-THC. By the same, procedure (-)-cannabidiol was bbtained on a preparative scale when greater than 0.5% boron trifluoride etherate or wet p-toluene-sulfonic acid was used. A mechanistic scheme is presented for this reaction. It is shown that cannabidiols are the key intermediates in this reaction and abnormal cannabidiol undergoes a retro-Friedel-Crafts reaction followed by recombination to normal cannabidiol. This retroreaction of 4 is rationalized on steric arguments. The isolation and study of products from this reaction give a much clearer understanding of the factors which control the outcome of acid-catalyzed reactions of p-mentha-2, 8-dien-1-ol and olivetol and have provided three new cannabinoids.

RAZDAN, R.K. and HANDRICK, G.R. Hashish. A stereospecific synthesis of (-)-delta-1-and (-)-delta-1(6)-tetrahydrocannabinols. Journal of the American Chemical Society 92: 6061-6062 (1970)

REGELSON, W., BUTLER. J.R., SCHULTZ, J., KIRK, T., PEEK, L. and GREEN, M.L. Delta-9-tetrahydrocannabinol (delta-9-THC) as an effective antidepressant and appetite stimulating agent in advanced cancer patients. Presented at the International Conference on the Pharmacology of Cannabis, National Institute on Drug Abuse, December 3-6, 1974.

RICHTER, J.A. and GOLDSTEIN, A. Effects of morphine and levorphanol on brain acetylcholine content in mice. The Journal of Pharmacology and Experimental Therapeutics 175(3): 685-691 (1970)

A modest increase in brain acetylcholine has been demonstrated with both morphine and levorphanol. It occurs in the "free" and "bound" fractions of acetylcholine but usually is largest and most significant in the latter. Similar increases were found in the pooled cerebral cortex and cerebellum and in the rest of the brain when these regions were examined separately. The inert stereoisomer dextrorphan, at a dose equal to an effective dose of levorphanol, did not cause an increase in brain acetylcholine. In mice made tolerant to the analgesic effect of levorphanol by repeated injection, only a small increase in brain acetylcholine occurred.

RICHTER, J.A. and GOLDSTEIN, A. Tolerance to opioid narcotics, II. Cellular tolerance to levorphanol in mouse brain. Proceedings of the National Academy of Sciences 66(3): 944-951 (July, 1970)

Mice were made tolerant to a large dose of levorphanol, a congener of morphine. Then 3H-levorphanol was given. The concentration of free, unchanged levorphanol in the brain water (ultrafiltrate) was found to be much higher than required to produce pharmacologic effects in nontolerant animals. The resuit indicates that tolerance arises from a diminished sensitivity to the drug at cellular or subcellular sites of drug action in the brain.

ROIZIN, L., HELPERN, M., BADEN, M.M., KAUFMAN, M. and AKAI, K. Toxosynpathies (a multifactor pathogenic concept). Drug Abuse: Current Concepts and Research. Edited by W. Keup. Springfield, Illinois: Charles C. Thomas, 1972. Pp. 97-11.6.

The simultaneous occurrence of multiple variable interractions intensify the toxogenetic or pathogenetic potentialities of the independent pharmacodynamic agent. Comparative studies of human and experimental drug toxicology have suggested that the tissue reaction patterns (relative tissue reaction scale) are the result of the interplay between the overall biological cofactors of the reacting organism (inherited and acquired) and the pharmacodynarnic properties of the chemical agents with the coparticipation of accessory of secondary cofactors (environmental, nutritional, socioecological, stressors, etc.).

ROSENBERG, H., KHANNA. K.L., TAKIDO. M. and PAUL, A.G. The biosynthesis of mescaline in Lophophora williamsii. Lloydia 32(3): 334-338 '(September, 1969)

Data are presented in support of a proposed pathway of biosynthesis of mescaline from dopamine.

ROSENGARTEN, H., MELLER, E. and FRIEDHOFF, A. J. In vitro enzymatic formation of melatonin by human erythrocytes. Research Communications in Chemical Pathology and Pharmacology 4(2): 457-465 (September, 1972)

An enzyme capable of forming melatonin from N-acetyl-serotonin was identified in the red blood cells of humans. The properties of this 0-methyltransferase are described with respect to distribution in blood, identity of the product formed and substrate specificity.

ROSENMAN, S.J. and SMITH, C.B. ^{14}C-catecholamine synthesis in mouse brain during morphine withdrawal. Nature 240: 153-155 (1972)

ROTH, R.H., WALTERS, J.R. and AGHAJANIAN, G. K. Effect of impulse flow on the release and synthesis of dopamine in the rat striatum. Frontiers in Catecholamine Research. Edited by E. Usdin and S.H. Synder. New York: Pergamon Press, 1973. Pp. 567-574.

In order to gain further insight into the mechanism responsible for the increase in dopamine (DA) produced by gamma-hydroxybutyrate (GHB), a compound which occurs as a natural metabolite of mammalian brain, the effect of GHB on the firing of dopaminergic neurons in the zona compacta of the substantia nigra was investigated by means of single unit recording techniques. These experiments revealed that GHB administered i.v. or i.p. decreased the firing of units localized to the DA containing cells present in the zona compacta of the substantia nigra. Cessation of impulse flow in DA neurons was found to result in a decrease in release and catabolism of DA and an increase in synthesis. These changes are reflected by a dramatic increase in the steady state levels of DA in the neuronal terminals. Once this new steady state level of DA is established the rate of synthesis returns to normal but is not inhibited as it is when DA levels are increased by inhibition of monamine oxidase (MAO). Drugs which are capable of stimulating DA receptors block this increase in DA observed after inhibition of impulse flow, suggesting that DA synthesis may in part be controlled by alterations in receptor activity.

SCHEEL-KRÜGER, J. Studies of various amphetamines, apomorphine and clonidine on body temperature and brain 5-hydroxytryptamine metabolism in rats. Psychopharmacologia 36: 189-202 (1974)

Amphetamine and various amphetamine derivatives, phenmetrazine, pipradrol, methylphenidate and NCA can increase the concentration of 5-HIAA in the rat brain without changing that of 5-HT. Metamphetamine produced a decrease in 5-HT and no effect on 5-HIAA whereas p-hydroxyamphetamine produced no effects on 5-HT and 5-HIAA. The experiments performed at different environmental temperatures (12-14°C. 21-22°C and 21-28-C) with simultaneous measurements of the body temperature indicate that no simple correlation exists between the drug induced hyperthermia and the effect on 5-HIAA. The amphetamine and phenmetrazine effect on 5-HIAA seems to be related to hyperthermia whereas the pipradrol and methylphenidate effect on 5-HIAA appears independent of hyperthermia. Apomorphine (2 x 2.5 mg/kg) which activates central dopamine receptors produced a significant increase in 5-HIAA whereas clonidine (0.5 mg/kg) which activates central noradrenaline receptors produced a significant decrease in 5-HIAA.

In conclusion, the effect of various amphetamines on 5-HT metabolism seems very complex in mechanism of action and might be related to hyperthermia, to a direct effect on 5-HT neurons and to the ratio between central dopamine/noradrenaline receptor activation of these drugs.

SCHEEL-KRÜGER, J., BRAESTRUP, C., EPLOV. L. and NIELSEN, M. The effect of amphetamine and reserpine on 3H-noradrenaline and its metabolites synthesized from intraventricular injected 3H-dopamine. Acta Pharmacologica et Toxicologica 35 (Supplement I): 50 11974)

The in vivo effect of amphetamine, reserpine, protriptyline, and pargyline has been studied on brain 3H-noradrenaline (3H-NA) and its quantitatively major metabolites. conjugated 3H-3-methoxy-4-hydroxyphenyleneglycol (3H-MOPEG) and conjugated 3H-3,4-dihydroxyphenyleneglycol (3H-DOPEG) synthesized after intraventricular (I.V.) injected 3H-dopamine (3H-DA). The present study shows characteristic metabolic changes after the abovementioned drugs: amphetamine produqed a strong decrease in 3H-DOPEG, whereas reserpine contrastingly produced a strong increase in 3H-DOPEG. Both drugs decreased 3H-NA and produced a relative increase in 3H-MOPEG. The most significant effect after protriptyline was a decrease in 3H-DOPEG. Pargyline produced a very strong decrease in both 3H-DOPEG and 3H-MOPEG.

The present results indicate that conjugated 3H-DOPEG formed,.from endogenous synthesized 3H-NA is a valuable indicatbr for drugs producing release (amphetamine) and uptake inhibition (amphetamine, protriptyline) of 3H-NA in central noradrenaline neurons. The result with reserpine provides evidence that non-stored 3H-NA to a large degree is metabolized (intraneuronally?) by monoamine-oxidase to 3H-DOPEG.

SCHEEL-KRÜGER. J., EPLOV. L. and NIELSEN. M. The effect. of prvtriptyline on the metabolism of labelled dopamine and noradrenaline in the rat brain. Psychopharmacologia 26 (Supplement): 45 (1972).

Protriptyline like other tricyclic antidepressant drugs has been shown to block the amine-uptake mechanism at the level of the cell membrane of central noradrenaline neurons, but not of dopamine neurons.

In order to get information on the effect of protriptyline on the metabolism of the catecholamines male Wistar rat received ^{3}H-L-DOPA (200 mu-C i.p.). The biochemical analyses were performed on the accumulation in the brain of labelled noradrenaline, the noradrenaline metabolites (NM, free & conjugated MOPEG), dopamine and the dopamine metabolites (MT. HVA and DOPAC). Prntriptyline' (10 mg/kg s.c.) and a peripheral decarboxylase inhibitor Ro 4-4602 (50 mg/kg i.p.) were given 30 min. hefore ^{3}H-L-DOPA.

Protriptyline produced a strong decrease of labelled noradrenaline and all noradrenaline metabolites. whereas no significant effect was found on labelled dopamine or the dopamine metabolites.

As possible explanations for this finding will be discussed: Spec.ific feed-back inhibition of noradrenaline biosynthesis, blockade of the uptake of ^{3}H-L-DOPA in noradrenaline neurons or reuptake inhibition of released dopamine formed in noradrenaline neurons.

SCHMIDT, M.J., HOPKINS, J.T., SCHMIDT. D.E. and ROBISON, G.A. Cyclic AMP in the brain: Effects of amphetamine and norepinephrine assessed through the use of microwave irradiation as a means of tissue fixation. Brain Research 42: 465-477 (1972)

SCHWEITZER, J.W. and FRIEDHOFF, A.J. The chemistry and detection of amphetamines. International Symposium on Drug Abuse. Edited by C.D.J. Zarafonetis. New York: Lea and Febinger, 1972. Pp. 233-241.

SCRAFANI, J.T. and CLOUET, D.H. The metabolic disposition of narcotic analgesic drugs: Biotransformations. Narcotic Drugs: Biochemical Pharmacology. Edited by D.H. Clouet. New York: Plenum Press, 1971. Pp. 137-158.

The biotransformations of narcotic drugs are analyzed. General patterns of metabolism of narcotic drugs are discussed with reference to chemical reactions, effects of species, sex, dose, and effects of route of administration. Sites of metabolism are described. Drugs analyzed include alpha-acetylmethadol, anileridine, codeine, cyclazocine, dextromethorphan, dihydromorphine, ethylmorphine, heroin, methadone, morphine, nalorphine, naloxone, normorphine, pentazocine, and propoxyphene. Metabolism in tolerant animals is discussed.

SCRAFANI. J. T., WILLIAMS, N. and CLOUET, D.H. The subcellular distribution of narcotic analgesics in rat brain. Committee on Problems of Drug Dependence. Washington, D.C.,: National Academy of Sciences, National Research Council, 1972.

Narcotic analgesics were taken up into rat brain synaptosomal fraction after both in vitro exposure and in vivo administration of the drug. Little or no bindingto other particulate fractions was observed in the experiments described here.

The uptake of the labeled drug into the synaptosomes of the different brain areas seemed to reflect the total uptake of the drug into the area although the percentage uptake varied enough to suggest that there were different narcotic analgesic binding properties for each area.

The differences in density of the peak of the binding of labeled drug were related to the differences in optical density.

SEGAL. D.S., KUCZENSKI, R. and MANDELL. A.J. Theoretical implications of drug-induced adaptive regulation for a biogenic amine hypothesis of affective disorder. Biological Psychiatry 9(2): 147-159 (1974)

Administration of the antidepressant tricyclic desmethylimipramine (DMI 10 mg/kg b.i.d. for 8 days) produced a significant decrease in the activity of regional brain tyrosine hydroxylase in noradrenergic pathways and a marginal decrease in the dopaminergic system of the rat brain. No change in the enzyme activity was observed 24 hr after a single administration of the same drug (25 mg/kg). In contrast, chronic reserpine treatment (0.5 mg/kg q.d. for 8 days) induced a delayed elevation of tryrosine hydroxylase activity of varying significance in the discrete brain regions examined. The functional significance of these apparent drug-induced compensatory responses is discussed in the context of a neurochemical theory of affective disorder that focuses on the role of adaptive regulatory mechanisms.

SEGELMAN, A.B., SOFIA. R.D., SEGELMAN, F.P., HARAKAL, J.J. and KNOBLOCH, L.C. Cannabis sativa L. (marijuana)V: Pharmacological evaluation of marijuana aqueous extract and volatile oil. Journal of Pharmaceutical Sciences 63(6): 962-964 (June, 1974)

The aqueous extract (marijuana tea) and volatile oil prepared from marijuana were compared with (-)-trans-delta-9-tetrahydrocannabinol for their effect on hexobarbital sleeping time and analgesic action in mice. All three substances prolonged hexobarbital sleeping time with an order of potency of (-)-trans-delta-9-tetrahydrocannabinol greater than aqueous extract greater than volatile oil. Each agent produced significant analgesic activity. However, the potencies of the aqueous extract and the volatile oil were similar to each other but only 1/200 that of (-)-trans-delta-9-tetrahydrocannabinol.

SETHY, V.H. and GESSNER. P.K. Effect of methanol on chloral hydrate metabolism in mice. The Pharmacologist 12:277 (1970)

Ethanol, when administered in combination with an equimolar amount of chloral hydrate (CH) to mice, increases the in vivo rate of reduction of CH to trichloroethanol (TCE) by 83% (Gesener and Cabana: Fed. Proc. 26 568, 1967) This led to the hypothesis that it is the faster rate of formation of the alcohol dehydrogenase-NADH complex in ethanol treated mice that is responsible for the faster rate of reduction of CH to TCE, the complex being a prerequisite of this reduction. Since methanol is metabolized in mice by the catalase-peroxidase system it should not lead to the formation of the alcohol dehydrogenase-NADH complex. Therefore the effect of methanol coadministration on the rate of CH disappearance provides a test of the above hypothesis. We find, upon determining the whole body levels of CH and TCE at various times following the i.p. administration of (I) 500 mg/kg of CH or (II) 500 mg/kg of CH plus an equimolar amount of methanol, that methanol coadministration has no significant effect on the rate of CH disappearance from the body. This supports the above hypothesis, We find, further that. TCH levels are higher following methanol coadministration. Analysis of this data suggests that methanol decreases significantly the rate of TCE disappearance.

SETHY, V.H. and WINTER, J.C. Effect of chronic treatment with mescaline upon tissue levels of the drug. Experientia 29: 571-572 (1973)

SHANI, A. and MECHOULAM, R.A new type of cannabinoid. Synthesis of Cannabielsoic Acid A by a novel photo-oxidative cyclisation. Chemical Communications, 1970. London, England: The Chemical Society. 1970. P. 273.

Two tricyclic dihydrobenzofuran cannabinoids have been isolated and one of them has been synthesized by an intramolecular photo-bxidative cyclisation which involves attack by a phenoxy-group and molecular oxygen on a double bond.

SHANI, A. and MECHOULAM, R. Photochemical reactions of cannabidiol. Cyclization to delta-1-THC and other transformations. Tetrahedron Letters 27: 601 (1971)

Irradiation of cannabidiol (I) in methanol gave mainly 1-methoxy-dihydrocannabidiol (II, both isomers). Irradiation of I in cyclohexane gave a complicated mixture from which, in addition to starting material, the following compounds were isolated: delta-1-tetrahydrocannabinol, delta-8-tetrahydrocannabinol. 8,9 dihydrocannabidiol (V), and 3'-cyclohexylcannabidiol (VI).

SHASKAN. E.G., HARASZTI, J.H. and SNYDER, S.H. Polyamines: Developmental alterations in regional disposition and metabolism in rat brain. Journal of Neurochemistry 20: 1443-1452 (1973)

The polyamines spermidine and spermine and the activity of the polyamine synthesizing enzyme, S-adenosyl-L-methionine (SAM) decarboxylase, were measured in regions of adult rat brains and during postnatal development. In the adult, although spermidine levels tended to correlate with the relative amounts of white matter in some areas, there were striking exceptions. SAM decarboxylase activity of the adult brain was higher than in most other mammalian tissues, although brain levels of polyamines were among the lowest. SAM decarboxylase activity appeared to be localized to cellular cytoplasm. Its activity increased with age in contrast to the levels of spermine, spermidine, DNA and RNA which decreased during postnatal development.

SHASKAN, E.G. and SNYDER, S.H. Kinetics of serotonin accumulation into slices from rat brain: Relationship to catecholamine uptake. The Journal of Pharmacology and Experimental Therapeutics 175(2): 404-418 (1970)

The accumulations of H^3-serotonin (H^3-5-HT) and H^3-norepinephrine (H^3-NE) into rat brain slices have been compared. Regional differences in accumulation of both amines occurred with highest uptakes for both amines in the corpus striatum. Other areas, however, showed significant differences with respect to amine accumulation after reserpine pretreatment and with respect to inhibition of uptake of the two amines by a variety of antidepressant drugs. Kinetic analyses indicated two components of 5-HT accumulation, one representing a high (uptake 1) and the other a low (uptake 2) affinity transport system. The K_l values for the competitive inhibition of dl-H^3-NE uptake by 5-HT were approximately equal to the K_m values for uptake of 2 of 5-HT, suggesting that the low affinity transport for 5-HT might involve uptake by the catecholamine transport system. Further evidence supporting the notion that 5-HT can be transported by cerebral catecholaminergic transport systems is as follows. 1) The relative potency of d- and l-NE and of dopamine in inhibiting 5-HT uptake in the hypothalamus and striatum paralleled their affinity for the catecholamine uptake process in these two areas. 2) Catecholamines were better inhibitors of H^3-5-HT uptake in the striatum when 5-HT concentration was increased to levels at which uptake 2 should predominate. Our findings suggest that doses of 5-HT administered into the brain in a variety of studies may enter catecholaminergic neurons in significant quantities.

SHASKAN, E.G. and SNYDER, S.H. Polyamine turnover in different regions of rat brain. Journal of Neurochemistry 20: 1453-1480 (1973)

The dynamics of the formation and disappearance of polyamines in rat brain have been examined after intraventricular administration of a tracer dose of (^{3}H) putrescine. After 2 days (^{3}H) putrescine was no longer detectable in any brain region examined. (^{3}H) Spermidine and (^{3}H) spermine were formed in all brain areas. In the midbrain, hypothalamus and cerebellum (regions which manifested the greatest initial accumulation of tritium) the specific radioactivity of spermidine declined with a half-life of 16-19 days. However, in areas with a low initial accumulation of tritium (the medulla-pons. internal capsule, cerebral cortex and corpus striatum) the specific radioactivity of spermidine changed very little between 2 and 19 days after the putrescine administration. Levels of (^{3}H) spermine increased continuously in all brain areas for a 14-day period after the putrescine injection.

SIMON, E.J., HILLER. J.M. and EDELMAN. I. Stereospecific binding of the potent narcotic, analgesic ^{3}H-etorphine to rat brain homogenate. Proceedings of the National Academy of Sciences 70: 1947 (1973)

Etorphine, the most potent narcotic analgesic known, was labeled with tritium by catalytic exchange. This drug exhibits stereospecific, saturable binding to rat-brain homogenate. At saturation, the stereospecific binding is 0.1-0.15 pmol/mg of protein. Specific binding is inhibited by high salt concentrations, sulfhydryl reagents, and proteolytic enzymes, but is unaffected by phospholipases A and C, sodium azide, sodium fluoride, and prostaglandins E and E_2. Competition for binding of (^{3}H) etorphine correlates with agonist and antagonist potencies. The stable, stereospecific binding of an active narcotic analgesic supports the existence of opiate receptors.

SLATKIN, D.J., DOORENBOS, N.J., HARRIS, L.S.. MASOUD. A.N., QUIMBY. M.W. and SCHIFF. P.L., JR. Chemical constituents of Cannabis sativa L. root. Journal of Pharmaceutical Sciences 60(12): 1891-1892 (December. 1971)

An extract of Cannabis sativa L. root yielded two pentacyclic triter-penes, friedelin and epifriedelanol, and N-(p-hydroxy-beta-phenylethyl)-p-hydroxy-trans-cinnamamide. Structures of the triterpenes were confirmed by preparation of derivatives and comparison to authentic friedelin. Epifriedelanol was also oxidized to friedelin. The amide was confirmed by synthesis.

SMITH, C.B., SHELDON, M.I., BEDNARCZYK. J.H. and VILLARREAL J.E. Morphine-induced increases in the incorporation of ^{14}C-tyrosine into ^{14}C-dopamine and ^{14}C-norepinephrine in the mouse brain: Antagonism by naloxone and tolerance. The Journal of Pharmacology and Experimental Therapeutics 180(3): 547-557 (1972)

The effects of morphine and levorphanol upon the incorporation of ^{14}C-tyrosine into ^{14}C-catecholamines in various tissues of the mouse were determined. Morphine, 100 mg/kg, increased the synthesis of ^{14}C-catecholamines in mouse brain and adrenals but not in heart or spleen. Morphine, 100 mg/kg, had no effect upon the free tyrosine or ^{14}C-tyrosine content of the mouse brain. d-Amphetamine, 10 mg/kg, did not increase the incorporation of ^{14}C-tyrosine into ^{14}C-catecholamines in these four tissues. Morphine, 100 mg/kg, and levorphanol, 10 mg/kg, nearly doubled the incorporation of ^{14}C-tyrosine into both ^{14}C- dopamine and ^{14}C-norepinephrine in the brain. Morphine-induced increases in ^{14}C-catecholamine synthesis occurred in the cerebral. cortex, diencephalon, striatum, brainstem and cerebellum. After repeated administration of either morphine, 100 mg/kg, or levorphanol, 30 mglkg, tolerance and cross-tolerance developed to the effects of these drugs upon the synthesis of ^{14}C-dopamine and ^{14}C-norepinephrine. Naloxone, a specific morphine antagonist, blocked the effects of morphine upon ^{14}C-dopamine and ^{14}C-norepinephrine synthesis. The present study suggests that the catecholamines may play an important role in the mechanisms by which narcotic analgesics produce certain specific effects.

SNYDER, S.H. Biochemically identified receptors in the design of new psychotropic drugs. Predictiveness in Psychopharmacology - Preclinical and Clinical Aspects. Edited by A. Sudilovsky, S. Gershon and B. Beer. New York: Raven Press, 1974.

SNYDER, S.H. Catecholamines and serotonin. Chapter 6 of Basic Neurochemistry. New York: Little, Brown and Company, Inc., 1972. Pp. 89-104.

The catecholamines. norepinephrine and dopamine, as well as the indole-amine, serotonin, are putative neurotransmitters in certain neuronal tracts in the brain. They occupy a uniquely important place in neurobiology because they are the only putative neurotransmitters whose localization in particular brain tracts has been established and whose relationship to specific animal or human behaviors has, at least in part, been worked out. Hence, a discussion of the neurochemistry of these compounds can integrate findings derived from electron microscopy, histo-chemistry, neurophysiology, enzymology, pharmacology, psychology, and even clinical psychiatry.

A great deal of information about catecholamines and serotonin had accumulated prior to knowledge of which neuronal tracts contained them or even whether they were localized in neurons at all. Nonetheless, for clarity's sake, it might be best to begin by presenting the histochemical observations that have delineated the neuronal systems which contain these compounds in the brain.

SNYDER, S.H. Catecholamines as mediators of drug effects in schizophrenia. The Neurosciences - Third Study Program. Edited by F.O. Schmitt and F.G. Worden, Cambridge, Massachusetts: MIT Press, 1974. Pp. 721-732.

Interactions of psychoactive drugs and neurotransmitters are a fruitful area for correlating biochemistry and behavior, especially as related to psychiatric illness. Ways in which psychoactive drugs influence neurotransmitters, particularly the biogenic amines, are reviewed. Emphasis is placed on a critical assessment of criteria for determining if a given "effect" of a drug represents its mode of action. Possible clues that such drug effects afford to the pathophysiology of various psychiatric disabilities in schizophrenia are evaluated.

SNYDER, S.H. Catecholamines in the brain as mediators of amphetamine psychosis. Archives of General Psychiatry 27: 169-179 (August, 1972)

Amphetamine psychosis appears to be a fruitful experimental model of paranoid schizophrenia or paranoid state. A variety of animal and human studies suggest that neurochemical mediation of certain behavioral effects of amphetamine in animals may reflect such mechanisms in human amphetamine psychosis. Specifically, locomotor stimulation appears attributable to central norepinephrine and stereotyped behavior to dopamine. while experiments with amphetamine isomers in man suggest a dopamine. while experiments with amphetamine isomers in man suggest a dopamine mediation of human amphetamine psychosis.

Pharmacological and stereochemical evidence suggest that clinical efficacy of phenothiazine drugs in the treatment of schizophrenia may be related to blockade of dopamine receptors. Taken together, these findings provoke the speculation that specific and distinct effects of amphetamines on dopamine and norepinephrine neurons may combine to account for major symptoms of amphetamine psychosis.

SNYDER, S.H. Neurotransmitter and drug receptors in the brain. Biochemical Pharmacology (in press)

SNYDER, S.H. Putative neurotransmitters in the brain: Selective neuronal uptake, subcellular localization, and interactions with centrally acting drugs. Biological Psychiatry 2: 367-389 (1970)

This review is concerned with specific neuronal uptake systems for different possible neurotransmitters in the brain and how advantage can be taken of these uptake systems to label nerve terminals with their transmitter in radioactive form. In these studies, kinetic analysis permitted a differentiation of the properties of the uptake system of the dopamine and norepinephrine neurons in the brain. These differences facilitated the prediction of new therapeutic agents in Parkinson's disease. Kinetic analysis also revealed that exogenous serotonin can enter catecholamine as well as serotonin neurons, and that these two uptakes can be discriminated. By labeling nerve terminals with radioactive neurotransmitters, some with carbon-14 and others with tritium, it was possible to develop methods to separate synaptosomes (pinched off nerve terminals) storing different neurotransmitters.

SNYDER, S.H. Stereoselective features of catecholamine disposition and their behavioral implications. Journal of Psychiatric Research 11: 1-10 (1974)

SNYDER, S.H. and BANERJEE, S.P. Amines in schizophrenia. Frontiers in Catecholamine Research 1133-1138 (1973)

This essay is not confined to catecholamines in schizophrenia, because to do so would convey the impression that other amines are irrelevant to the disease. Some drug actions suggest a role for dopamine; others implicate the indoleamines. The 'dopamine story' derives from the influences of antischizophrenic phenothiazines and butyrophenones upon the synaptic activities of dopamine and studies of amphetamine psychosis as a model schizophrenia mediated via brain dopamine. Aspects of indoleamines relevant to schizophrenia are: (a) the psychotomimetic actions of indoleamine-related psychedelic drugs, and (b) the existence of enzymes capable of methylating indoleamines to form psychedelic drugs in the human body.

SNYDER, S.H., BANERJEE, S.P., YAMAMURA, H.I. and GREENBERG, D. Drugs, neurotransmitters, and schizophrenia. Science 184:243-1253 (June, 1974)

Of various biochemical approaches to the study of schizophrenia, the investigation of brain neurotransmitter interactions with psychotropic drugs has proved most productive in recent years. Analyses of the mechanism of the antischizophrenic activities of the phenothiazines and the ability of amphetamines to worsen schizophrenic symptoms and elicit a schizophrenia-like psychosis have focused attention upon dopamine in the brain. Findings of reduced platelet monoamine oxidase and brain dopamine beta-hydroxylase activities in schizophrenics, represent enticing but tentative data that would be consistent with a "dopamine hypothesis." The ability of psychedelic drugs to mimic the symptoms of certain early stages of schizophrenia remains a promising lead. An enzymatic activity that utilizes the methly group of 5-methyltetrahydrofolic acid to O-methylate and N-methylate phenylethylamines and indoleamines, thereby forming psychotomimetic drugs, is a possible mechanism for the production of such compounds in the mammalian brain. None of these approaches yet affords the definitive "answer" to the riddle of schizophrenia, and roles for other neurotransmitters, such as acetylcholine and gamma-aminobutyric acid are possible.

SNYDER, S.H., PERT, C.B. and PASTERNAK, G.W. The opiate receptor. Annals of Internal Medicine 81 (4): 534-540 (October, 1974)

Binding of radioactive opiates and opiate antagonists to the opiate receptor in the brain and other tissues can be shown. This binding mediates the pharmacologic effects of the drugs. The regional distribution of the opiate receptor in monkey and human brain parallels the motivational affective pathways of pain perception and comprises several limbic system structures. In subcellular fractionation experiments, the opiate receptor is localized to synaptic membranes. The influence of sodium onreceptor binding permits predictions of the extent to which a drug possesses opiate agonist, antagonist, or mixed properties. The simple, sensitive, and specific opiate receptor binding assay facilitates development of pure opiate antagonists for treating narcotic addiction and mixed agonist-antagonist agents with potential as nonaddicting analgesics.

SNYDER, S.H., YOUNG. A.B., BENNETT. J.P. and MULDER, A.H. Synaptic biochemistry of amino acids. Federation Proceedings 32(10): 2039-2047 (October, 1973)

Neurophysiological research has suggested that certain naturally occurring amino acids possess transmitter properties in the mammalian central nervous system. L-glutamic and L-aspartic acids act as excitatory agents on the postsynaptic membranes of many neurons. Gamma-amino butyric acid and glycine mimic natural inhibitory transmitters in the cerebral cortex, and brainstem and spinal cord, respecively. For the transmitter candidates L-glutamic and L-aspartic acids in cerebral cortex and spinal cord, and glycine only in the spinal cord and brainstem we found unique, sodium-dependent, high affinity transport systems in synaptosomes. Subcellular fractionation demonstrated unique synaptosomal populations which accumulate these amino acids. These amino acids are selectively released from central nervous system slices by K^+ depolarization. For L-proline, a previously unsuspected transmitter, we found a unique, sodium-dependent, high affinity transport system in cerebral cortical synaptosomes and selective release by K^+ depolarization. Other nontransmitter candidate amino acids possessed none of these neurochemical properties. Strychnine, a specific postsynaptic antagonist of glycine in the central nervous system binds to fractions rich in synaptic membranes and its binding appears to represent an interaction with the postsynaptic glycine receptor. The displacement of strychnine binding by glycine and glycine analogs parallels glycinelike neurophysiological activity. The regional distribution of strychnine binding correlates with endogenous glycine levels and with the neurophysiological actions of glycine.

SPAULDING, T.C., FORD, R.D., DEWEY, W.L., McMILLAN, D.E. and HARRIS, L.S. Some pharmacological effects of phenitrone and its interaction with delta-9-THC. European Journal of Pharmacology 19: 310-317 (1972)

We have investigated the pharmacological effects of phenitrone (3-(hexahydro-1-H-azepin-1-yl)-3'-nitropropiophenone HCl), a compound which has been reported to block and reverse the toxic and behavioral effects of hashish in dogs. There was no apparent blockage of cannabinoid-like activity when phenitrone was administered prior to or concomitantly with delta-8-THC, or the NIMH marihuana distillate in dogs and pigeons. However, phenitrone produced bizarre behavioral effects in dogs when given at a dose of 40 mg/kg and decreased the rate of conditioned key pecking for food at doses above 18 mg/kg in pigeons. When phenitrone and delta-9-THC were given simultaneously, a dose-dependent inhibition of delta-9-THC-induced activity in the mouse tail-flick test was observed. Phenitrone did not block hypothermia produced by either a single injection or 5 daily injections of delta-9-THC in mice. Phenitrone also produced a decrease in spontaneous activity and had an LD_{50} of 175 mg/kg i.p. in mice.

SPAULDING, T.C., MINIUM, L., KOTAKE, A.N. and TAKEMORI, A.E. The effect of diazepam on the metabolism of methadone by the liver of methadone-dependent rats. Drug Metabolism and Disposition 2(5): 458-463 (1974)

The N-demethylation of methadone by 9000g supernatant fractions of hepatic homogenates was investigated in methadone-dependent rats. In these studies rats were administered methadone hydrochloride by allowing free access to the drug dissolved in the drinking water (0.5 mg/ml). Rats in the control group ingested tap water. The V_{max} of N-demethylation by liver supernatant fractions from methadone-dependent rats was 40-50% higher than that from control animals, whereas the K_m values did not differ significantly. The increase in V_{max} after chronic administration of methadone was not reflected by alteration of either the amount of cytochrome P-450 or the ethyl isocyanide binding. Diazepam was found to be a competitive inhibitor of N-demethylation of methadone with a K_i of 1. 7 X 10^{-4} M when incubated with hepatic supernatant fractions from control rats. However, diazepam was an uncompetitive inhibitor when incubated with supernatant fractions from livers of methadone-dependent rats. These data indicate that, unlike other opioid narcotics, methadone increased its own metabolism upon chronic treatment. Further, diazepam was shown to be a fairly effective inhibitor of the N-demethylation of methadone which may explain in part the enhanced effect of methadone observed in narcotic addicts when the combination is taken.

SPAULDING, T.C. and TAKEMORI, A.E. Studies on N-demethylation of methadone in methadone-dependent rats. The Pharmacologist 16: 194 (1974)

When a methadone (M) solution (0.5 mg/ml) was substituted for drinking water in rats, withdrawal signs could be precipitated by naloxone after 5 days of drinking. The N-demethylation of M by 9,000 x g supernatants of hepatic homogenates was investigated in these M-dependent rats. V_{max} was increased by 40-50% while the apparent K_m remained unchanged when compared to control values (V_{max} nmoles/mg/hr; K_m= 1.78 x 10^{-4} M). The content of cytochrome P-450/mg microsomal protein for control and M-dependent rats was 0.730 ± .034 and 0.732 ± .055 respectively and the ethyl isocyanide difference spectrum for control and dependent rats was 0.431 and 0.471 ± .026 respectively. Diazepam (D) at a concentration of 5.9 x 10^{-5} or 1.57 x 10^{-4} M was found to be a competitive inhibitor of the N-demethylation of M with a Ki of 1.71 x 10^{-4}M. However, D became an uncompetitive inhibitor when incubated with supernatants from livers of M-dependent rats. Unlike other opioid narcotics, M increased its own metabolism upon chronic treatment with no change in microsomal P-450. D was shown to be a fairly effective inhibitor of the N-demethylation of M which may explain in part the enhanced effect of M observed in narcotic addicts when the combination was taken.

STOELTING, R.K., MARTZ R.C., GARTNER, J., CREASSER, C., BROWN, D.J. and FARNEY, R.B. Effects of delta-9-tetrahydrocannabinol on halothane MAC in dogs. Anesthesiology 38(6): 521-524 (June, 1973)

The effects of acute and subacute administration of delta-9-tetrahydrocannabinol (THC) on halothane requirements (MAC) in four groups of dogs were measured. THC administered intravenously produced a dose-related alteration in MAC. THC, 0.1 mg/kg, did not alter MAC 1, 3, or 24 hours after its administration. THC, 0.5 mg/kg, decreased MAC 32 per cent (P less than 0.05) 1 hour after injection, but MAC was not significantly different from control after 3 and 24 hours. MAC was decreased 42, 36, and 18 per cent (P less than 0.05) from control 1, 3, and 24 hours after 2.0 mg/kg THC. MAC was not changed from control 24 hours after four daily injections of 0.5 mg/kg THC.

Student Association for the Study of Hallucinogens, Inc. MDA. STASH Capsules 5(1) (February, 1973)

Student Association for the Study of Hallucinogens, Inc. STASH fact sheet on cocaine. Grassroots (February, 1972 supplement)

Student Association for the Study of Hallucinogens, Inc. STASH fact sheet on DOM ("STP"). Grassroots (July, 1972 supplement)

Student Association for the Study of Hallucinogens, Inc. STASH fact sheet on methadone. Grassroots (May, 1972 supplement)

Student Association for the Study of Hallucinogens, Inc. STASH fact sheet on opioids. Grassroots (November, 1972 supplement)

Student Association for the Study of Hallucinogens. Inc. STASH fact sheet on psilocybin. Grassroots (August, 1972 supplement)

Student Association for the Study of Hallcinogens, Inc. STASH notes: A mini-review of the 1973 marijuana literature, Part I. STASH Capsules 6(2) (March-April, 1974)

Student Association for the Study of Hallucinogens, Inc. STASH notes: A mini-review of the 1973 marijuana literature, Part II. STASH Capsules 6(3) (May-June, 1974)

Student Association for the Study of Hallucinogens, Inc. STASH notes: Methaqualone. STASH Capsules 5(3) (May-June, 1973)

Student Association for the Study of Hallucinogens, Inc. STASH notes: Phenyclidine (PCP). STASH Capsules 5(2) (April, 1973)

TAKEMORI. A.E., WARD, A., PORTOGHESE, P.A. and TELAND. V.G. Potential nonequilibrium analgesic receptor inactivators. Further pharmacologic studies of N-acylanileridines. Journal of Medicinal Chemistry 17(10): 1051-1054 (1974)

The antagonistic property of ethyl p-(4-ethoxycarbonyl-4-phenyl-1 piperidinoethyl) fumaranilate (5) was investigated. Compound 5 was found to antagonize morphine analgesia in complex manner which could not be described as a simple competitive or noncompetitive type. The antagonism, however, lasted for over 6 hr suggesting that 5 has a high affinity for the analgesic receptors. Compound 5 appeared to possess dependence liability in the single-dose suppression test. In the electrically stimulated isolated guinea pig ileum, 5 acted like an agonist. No antagonistic activity of 5 was apparent in the latter two tests.

TAKIDO, M. KHANNA, K.L. and PAUL, A.G. New synthesis of rac. anhalonidine and rac. pellotine. Journal of Pharmaceutical Sciences 59(2): 271-273 (February, 1970)

A new synthesis of rac. anhalonidine and rac. pellotine is reported. The procedure, a modification of the method of Bobbitt et.al. for the synthesis of 1, 2, 3, 4-tetrahydroisoquinolines, is simpler and gives better yields than those previously reported.

TAYLOR, J.F. Development aspects of the transport of meperidine into rat brain in vivo. Federation Proceedings 29: 686 (1970)

The development of a blood-brain barrier to meperidme in young rats has not been detected pharmacologically, thus it was investigated by drug distribution studies. Meperidine (25 mg/kg) was injected into 16- and 32-day old rats which were then decapitated at 5 min. intervals up to 30 min. after drug administration. Brain and plasma, obtained at time of sacrifice and analyzed by gas chromatography, contained maximum amounts of the drug at 10 min. after the injection. The average concs. of meperidine in the brain and plasma of 16-day old rats (41.5 ug/g and 4 ug/ml at 10 min.) were significantly higher than those of 32-day old animals (25 ug/g and 2.8 ug/ml at 10 mm.). However, the average ratios of brainplasma cones. of drug were similar (10.4:1 and 9:1). indicating little difference between the 2 groups with respect to meperidine transport from plasma to brain. With gastroenemius muscle, the tissue: plasma concs. of drug were the same in both age groups, the low values (2:1 to 3:1 at 10 mm.) indicating the much greater ability of the brain to concentrate meperidine. In 16-day old rats whose drug metabolizing ability was induced by phenobarbital pretreatment the conc. of meperidine in brain 10 min. after injection was lower than in untreated animals of the same age.

TAYLOR, K.M. and SNYDER, S.H. Differential effects of D-and L-amphetamine on behavior and on catecholamine disposition in dopamine and norepinephrine containing neurons of rat brain. Brain Research 28: 295-309 (1971)

We have compared the effects of D- and L-amphetamine on the disposition of intraventricularly administered (^{3}H) norepinephrine and (^{3}H) dopamine and on endogenous catecholamine in various regions of the rat brain. In behavioral experiments the effects of D- and L-amphetamine on locomotor activity and on compulsive gnawing behavior were also compared. In brain areas where norepinephrine is the predominant catecholamine, D-amphetamine but not its L-isomer inhibited (^{3}H) catecholamine accumulation and lowered endogenous norepinephrine levels. In the corpus striatum, a dopaminergic brain region, both D- and L-amphetamine markedly reduced accumulation of (^{3}H) catecholamines. D-Amphetamine was 10 times as potent as L-amphetamine in enhancing locomotor activity. but was only twice as active in evoking compulsive gnawing behavior. Our results suggest that brain norepinephrine is selectively involved in mediating amphetamine-induced locomotor stimulation while a dopaminergic component may participate in eliciting the compulsive gnawing syndrome.

TAYLOR, K.M. and SNYDER, S.H. Dynamics of the regulation of histamine levels in mouse brain. Journal of Neurochemistry 19: 341-352 (1972)

The intraperitoneal administration of L-histidine in a dose of 1000 mg/kg increased three-fold the whole brain levels of histamine in the mouse. This increase was evident in all brain regions except the medulla oblongata-pons. The subcellular localization of histamine and histidine was the same in mice administered L-histidine as in saline-treated animals. Cold exposure and restraint further augmented the elevation of histamine elicited by histidine treatment. Alpha-Hydrazino-histidine and 4-bromo-3-hydroxy-benzyloxyamine (NSD-1055) but not alpha-methyl-DOPA inhibited histidine decarboxylase (EC 4.1.1.22) activity in mouse brain homogenates and prevented the increase in brain histamine after histidine administration. NSD-1055 and alpha hydrazino-histidine also lowered brain levels of histamine by 50 per cent. NSD-1055 lowered whole brain levels of histamine rapidly, with a half-life for the depletable histamine pool of about 5 mm. Assuming that inhibition of histidine decarboxylase accounted for the reduction in histamine, then the rate of histamine decline reflects the rate of histamine turnover, and our results suggest that a portion of mouse brain histamine turns over quite rapidly. Reserpine lowered brain levels of histamine by about 50 per cent, whereas the antihistammic agent, dexbrompheniramine, and sodium pentobarbital elevated histamine levels.

TAYLOR, K.M. and SNYDER, S.H. Histamine in rat brain: Sensitive assay of endogenous levels, formation in vivo and lowering by inhibitors of histidine decarboxylase. The Journal of Pharmacology and Experimental Therapeutics 173(3): 619-633 (1971)

The sensitivity of an enzymatic isotopic method for histamine was enhanced so that as little as 0.2 ng in tissue samples could be measured. With this method histamine was measured in regions of the rat brain. Concentrations ranged from 177 ng/g in the hypothalamus to 22 ng/g in the cerebellum. ^{3}H-histamine was measured reliably in the hypothalamus after the intraventricular injection of ^{3}H-histidine. The formation of hypothalamic ^{3}H-histamine from ^{3}H-histidine was inhibited by alpha-hydrazinohistidine and 4-bromo-3-hydroxybenzyloxamine (NSD-1055) but not by alpha-methly-dopa, suggesting that histamine is formed by the action of a specific histidine decarboxylase. Alpha-hydrazinohistidine and NSD-1055 but not alpha-methyldopa maximally lowered endogenous histamine in several brain regions 35 to 40%, with a half-life of depletion of about five minutes. This suggests that a portion of brain histamine turns over at'a very rapid rate,

TELLER, D.N. and DENBER, H.C.B. Binding of psychotropic drugs to soluble proteins. Neuro-Psychopharmacology . Edited by H. Brill. New York: Excerpta Medica Foundation, 1967. P. 1177.

Studies of fluorescence polarization and quenching of chlorpromazine, thioproperazine, promazine, prochlorperazine and LSD-25 indicated methods for the measurement of drug binding to proteins. Titration of fluorescence quenching of human serum fractions, bovine ribonuclease preparations, and purified enzymes from various sources, can be performed with 10^{-9} mole or less of the drug and protein. Results indicate that the phenothiazine drugs bind preferentially to proteins possessing oxidative activity. Drug binding is further enhanced in the presence of reduced pyridine nucleotide coenzymes.

Additional, non-stoichiometric and loose binding (or absorption), can be observed and measured. Tightly coupled drug protein complexes have been prepared from polyacrylamide gel columns. In the case of LSD-human albumin, the binding shows low dissociation at 8 mu-g LSD/mg protein. The phenothiazine drugs bind to a greater extent than LSD, and dissociate (thioproperazine greater than prochlorperazine greater than promazine greater than chlorpromazine) in the oxidized state. Binding of the psychotropic drugs to particulate protein (subcellular organelles) is several times as great as to the soluble proteins.

TELLER, D.N., DENBER, H.C.B. and KOPAC, M.J. Binding of chlorpromazine and thioproperazine in vitro -- I. Results of centrifugation methods with tissue and mitochondria from rat liver and human leukocytes. Biochemical Pharmacology 16: 1397-1410 (1967)

Binding of two phenothiazine neuroleptics, chlorpromazine (CPZ) and thioproperazine (TPZ) was studied with rat liver and human leukocytes as sources of tissue and mitochondria. After 10 min of incubation at 24° in 15 or 30 mu-g CPZ/ml Hank's solution, rat liver bound 66-88 per cent, whereas human leukocytes bound 27-29 per cent of the drug. Eight sequential centrifugal washings of the rat liver tissue released 30 per cent of the CPZ, but under the same conditions human leukocytes released 84-100 per cent of the bound drug. In contrast, weobserved no difference in mitochondrial binding due to difference between tissues. Liver and leukocyte mitochondria were centrifuged at 8° through linear sucrose density gradients that contained a constant concentration of 15 or 30 mu-g phenothiazine/ml. After 5 min of centrifugation through a sucrose gradient containing 15 mu-g CPZ/ml, 3.7 mu-g CPZ/ml was bound/mg mitochondrial protein; after 15 min. 5.3 mu-g drug/ml was bound/mg protein. With 30 mu-g CPZ/ml in the gradient, 2.2 and 9.9 mu-g of drug/ml were bound/mg protein after 5 and 15 min, respectively. If TPZ, at either 15 or 30 mu-g/ml, was present in the gradient, 3.0 and 4.4 mu-g of drug/ml were bound/mg protein after 5 and 15 min. Cooperative effects on binding by the mitochondria and the drugs were observed as a function of duration of exposure at 8°. Significant quantities of each drug, measured spectrophotofluorinetrically, were removed from solution by the mitochondrial suspensions.

TRUITT. E.B., JR. and ANDERSON, S.M. Biogenic amine alterations produced in the brain by tetrahydrocannabinols and their metabolites. Annals of the New York Academy of Sciences 191: 68-73 (1971)

The involvement of biogenic amines in the brain effects of tetrahydrocannabinols has been reviewed. It appears on the basis of equilibrium-level changes that Cannabis extracts and delta-9-tetrahydrocannabinol (delta-9-THC) significantly elevate brain serotonin (5-HT) levels while producing a slight fall or no significant effect on norepinephrine (NE) except at high doses, when a rise occurs. Preliminary estimates of turnover times suggest that THC slows both 5-HT and NE turnover. More complete studies of biogenic amine function will be required before the final mechanisms of THC on the brain are elucidated.

TRUITT, E.B., JR, and ANDERSON, S.M. The role of biogenic amines in the central actions of tetrahydrocannabinols and their metabolites. Acta Pharmaceutica Suecica 8: 696-697 (1971)

Earlier studies using equilibrium levels have shown greater changes in the whole brain content of serotonin (5-HT) rather than catecholamines, noradrenaline (NA) and dopamine (DA). Several investigators have found an elevation of 5-HT with one exception. In contrast, no marked changes have been noted in whole brain levels of NA. However, the use of turnover analysis in this investigation shows that changes occur in NA metabolism as well.

TURANO, P., MARCH, J.E., TURNER, W.J. and MERLIS, S. Qualitative and quantitative report on chlorpromazine and metabolites in plasma, erythrocytes and erythrocyte washings from chronically medicated schizophrenic patients. Journal of Medicine 3: 109-120 (1972)

Qualitative and quantitative analysis of blood plasma, of erythrocyte washings, and of hemolysates of 22 schizophrenics under long-term chlorpromazine therapy was carried out by thin layer chromatography of dichloromethane extracts before and after hydrolysis of samples obtained at 1.5 h after morning medication, and again 12-15 h after evening medication. Chlorpromazine, five nonhydroxylated and six hydroxylated metabolites, could be identified. The major metabolites found were'chlorpromazine, Nor_2chlorpromazine and their sulfoxides in plasma and washings, while 7-hydroxychlorpromazine and its sulfoxide appeared as glucuronides in plasma and washings, but free and associated with 7-hydroxy Nor_1- and Nor_2-chlorpromazine in hemolysates. Quantitatively, plasma levels vary quite widely between individuals, but rise with increasing dose.

TURANO, P., TURNER, W.J. and DONATO, D. Further studies of chlorpromazine metabolism in schizophrenic men. The Phenothiazines and Structurally Related Drugs. Edited by I.S. Forrest, C.J. Carr and E. Usdin. New York: Raven Press, 1974.

Nonenzymatic oxidation of CPZ and 7-OH-CPZ was shown to occur at each of the steps in preparation of biological materials for quantitation by TLC or GC. The oxidations, in absence of Fe^{2+}, in light or in dark, in water or in organic solvents, led to monodesmethylation, sulfoxidation, and formation of N-S dioxides. In water, CPZ also gave rise probably to acidic derivatives. In water or diethyl ether, 3,7-dihydroxy-CPZ arose from 7-OH-CPZ. Ascorbic acid increased sulfoxide formation but restricted further oxidation.

TURANO, P., TURNER, W.J. and MANIAN, AA. Thin-layer chromatography of chlorpromazine metabolites. Attempt to identify each of the metabolites appearing in blood, urine and feces of chronically medicated schizophrenics. Journal of Chromatography 75: 277-293 (1973)

For abstract, see Section I. Methodology of Drug Research.

TURK, R.F., DEWEY, W.L. and HARRIS, L.S. Excretion of trans-delta-9-tetrahydrocannabinol and its metabolites in intact and bile-cannulated rats. Journal of Pharmaceutical Sciences 62(5): 737-740 (1973)

Tritiated delta-9-tetrahydrocannabinol (I) was administered both orally and intravenously to groups of bile duct cannulated rats and those with their bile duct intact. From 55.8 to 66.9 percent of the total radioactivity was excreted during the 96 hr period following administration. The excretion of radioactivity was minimal in each group beyond 48 hr after drug administration. The major route of excretion following the intravenous administration in bile duct-cannulated rats was by way of bile (59.4 percent; feces, 2.7 percent), whereas more radioactivity was excreted in feces (41.5 percent) than bile (21.5 percent) when the drug was given orally. This extract was found to contain I by thin layer chromatography (TLC) and gas liquid chromatography analysis. After intravenous administration, the radioactivity in the feces was not extractable in petroleum ether but appeared in ether, methanol, and water extracts. TLC confirmed that the radioactivity in these solvents was associated with metabolites of I. Bile contained mainly metabolites of I, as did the urine. Less than 10 percent of the radioactivity was excreted in the urine of each group of rats.

TURNER, C.E. and HADLEY, K. Constituents of Cannabis sativa L. II: Absence of cannabidiol in an African variant. Journal of Pharmaceutical Sciences 62(2): 251-255 (February, 1973)

Cannabidiol is shown to be absent in an African variant of Cannabis sativa L. (marijuana) grown in Mississippi. TLC, GC, and GC-mass spectrometry were used for identification. The absence of cannabidiol in a variant of African Cannabis questions the validity of published biosyntheses of the cannabinoids.

TURNER, C.E. and HADLEY, K.W. Constituents of Cannabis sativa L. III: Clear and discrete separation of cannabidiol and cannabichromene. Journal of Pharmaceutical Sciences 82(7): 1083-1086 (July, 1973)

Synthetic cannabidiol and cannabichromene were discretely separated by GLC using their trimethylsilyl ether derivatives. The mono and disilylated derivatives of cannabidiol were identified. This procedure was utilized in the analysis of Cannabis sativa L.

TURNER, C.E., HADLEY, K.W. and DAVIS, K.H., JR. Constituents of Cannabis sativa L. V. Stability of an analytical sample extracted with chloroform. Acta Pharmaceutica Jugoslavica 23(2): 89-94 (1973)

For abstract, see Section I. Methodology of Drug Research.

TURNER, C.E., HADLEY, K.W. and FETTERMAN, P.S. Constituents of Cannabis sativa L. VI: Propyl homologs in samples of known geographical origin. Journal of Pharmaceutical Sciences 62(10): 1739-1741 (October, 1973)

TURNER, C.E., HADLEY, K.W., FETTERMAN, P.S., DOORENBOS, N.J., QUIMBY, M.W. and WALLER, C. Constituents of Cannabis sativa L. IV: Stability of cannabinoids in stored plant material. Journal of Pharmaceutical Sciences 62(10): 1601-1605 (October, 1973).

The (-)-delta-9-trans-tetrahydrocannabinol content of Cannabis sativa L. stored at -18, 4, and 22 ± 1° decomposed at a rate of 3.83, 5.38, and 6.92%, respectively, per year, whereas the material stored at 37 and 50° showed considerable decomposition. C. sativa L. stored in the absence of direct light at -18, 4, and 22 ± 1° was more stable than cannabis stored under nitrogen. These data indicate that for normal research use, storage under nitrogen at 0° is not mandatory. Cannabinol is not the only decomposition product of (-)-delta-9-trans-tetrahydrocannabinol. Tentative evidence supports the possible formation of hexahydrocannabinol as a decomposition product in stored C. sativa L.

TURNER, W.J., TURANO, P.A. and MARCH, J.E. Quantitative determination of chlorpromazine metabolites in urine. Clinical Chemistry 16(11): 916-921 (1970)

For abstract, see Section I. Methodology of Drug Research.

VALERINO, D.M., VESELL, E.S., AURORI, K.C. and JOHNSON. A.O. Effects of various barbiturates on hepatic microsomal enzymes. A comparative study. Drug Metabolism and Disposition 2(5): 448-457 (1974)

Six barbiturates were compared with respect to the extent that they stimulated hepatic microsomal enzymes of mature male rats after 1, 3, 7, and 14 days of daily ip drug administration. Phenobarbital, pentobarbital, secobarbital, thiopental, and barbital stimulated ethylmorphine N-demethylase and aniline hydroxylase activities and increased microsomal cytochrome P-450 content. Considerable temporal differences occurred among these barbiturates in maximal stimulatory responses. Stimulatory responses approached or exceeded 200% of control values after 3,7, and 14 days of daily phenobarbital (100 mg/kg) administration. Responses exceeding 200% of control values were elicited by barbital (150 mg/kg) during the 14-day observation period. Considerably less stimulation occurred with pentobarbital, secobarbital, and thiopental, and none with hexobarbital. Compared on a molar basis, phenobarbital was the most potent stimulatory agent for each microsomal parameter after three daily ip injections. Correlation coefficients between partition coefficients for these six barbiturates and their stimulatory potencies were less than 0.45 and were considered not to be biologically significant. Oral administration of phenobarbital (100 mg/kg), secobarbital (75 mg/kg), or hexobarbital (150 mg/kg) for 3 consecutive days did not significantly alter the stimulatory response of an identical ip dose of each barbiturate. An association appears to exist between plasma half-lives of phenobarbital (10.1 hr), pentobarbital (2.3 hr), and hexobarbital (36. 2 min) and their stimulatory potencies. Hepatic radioactivity 24 hr after administration of these three barbiturates was directly related to their stimulatory potencies.

VALERINO, D.M., VESELL, E.S., JOHNSON, A.O. and AURORI, K.C. Effects of various centrally active drugs on hepatic microsomal enzymes: A comparative study. Drug Metabolism and Disposition 1(5): 669-678 (1973)

The extent to which six centrally active drugs stimulated hepatic microsomal enzymes of mature male rats was compared. Of the three parameters examined, diphenylhydantoin enhanced only ethylmorphine N-demethylase activity and cytochrome P-450 content, whereas the other five drugs stimulated aniline hydroxylase activity as well. By measuring changes in these microsomal systems after 3, 7, and 14 days of drug administration, the stimulatory capacities of the six drugs were determined and compared. The stimulatory capacity of each drug was related to its dose and varied considerably in the temporal pattern exhibited. Near maximal stimulation of all three parameters occurred very early with phenobarbital (after three daily injections), whereas chlorpromazine, diazepam, meprobamate, and diphenylhydantoin produced maximal stimulatory responses only after 7-14 daily injections. Daily administration of high doses of diphenylhydantoin or ethanol decreased the activity or content of at least one of the three microsomal systems under investigation. On a molar basis, phenobarbital was the most potent stimulatory agent after three daily injections; at this time the other five drugs were generally similar to one another. In the doses employed in this study, only phenobarbital produced more than 2-fold stimulation of all three microsomal parameters. After 7 days of administration, diphenylhydantoin elevated ethylmorphine N-demethylase activity 240% above control values.

VANVUNAKIS, H., FARROW, J.T., GJIKA, H.B. and LEVINE, L. Specificity of the antibody receptor site to D-lysergamide: Model of a physiological receptor for lysergic acid diethylsmide. Proceedings of the National Academy of Sciences 68(7): 1483-1487 (July, 1971)

Antibodies to D-lysergic acid have been produced in rabbits and guinea pigs and a radioimmuno-assay for the hapten was developed. The specificity of this lysergamide-antilysergamide reaction was determined by competitive binding with unlabeled lysergic acid diethylamide (LSD), psychotomimetic drugs, neurotransmitters, and other compounds with diverse structures. LSD and several related ergot alkaloids were potent competitors, three to seven times more potent than lysergic acid itself. The N, N-dimethyl derivatives of several compounds, including tryptamine, 5-hydroxytryptamine, 4-hydroxytryptamine, 5-methoxytryptamine, tyramine, and mescaline were only about ten times less effective than lysergic acid, even though these compounds lack some of the ring systems of lysergic acid. The pattern of inhibition by related compounds with various substituents suggests that the antibody receptor site recognizes structural features resembling the LSD molecule. In particular, the aromatic nucleus and the dimethylated ethylamine side chain in phenylethylamine and tryptamine derivatives may assume in solution a conformation resembling ring A and the methylated nitrogen in ring C of LSD. Among the tryptamine derivatives, a large percentage of the most potent competitors are also psychotomimetic compounds.

WAINER, B.H., FITCH, F.W., FRIED, J. and ROTHBERG, R.M. Immunological studies of opioids: Specificities of antibodies against codeine and hydromorphone. Clinical Immunology and Immunopathology 3(2): 155-170 (1974)

For abstract, see Section I. Methodology of Drug Research,

WAINER, B.H., FITCH, F.W., FRIED, J. and ROTHBERG, R.M. Immunochemical studies of opioids: Specifications of antibodies against codeine and hydromorphone. Clinical Immunology and Immunopathology 3: 155 (1974)

Two new immunogenic opioid-protein conjugates were prepared. Codeine-6-hemisuccinate was synthesized from the reaction of codeine with succinic anhydride and hydromorphone-6-carboxymethyloxime was synthesized from the reaction of hydromorphone with alpha-aminoxyacetic acid. Both opioids were attached covalently to bovine serum albumin using the mixed anhydride procedure and employed as immunogens in rabbits. Antibody measured by the ammonium sulfate method showed increases in titer and avidity following subsequent immunizations. The specificities of both antisera were studied by competitively inhibiting the binding of labeled opioid to antibody by the prior addition of increasing concentrations of various unlabeled opioids. The ranges of immunoreactivity of both antisera were different and corresponded closely to the structures of the respective immunizing haptens. These observations suggest that antibodies prepared against codeine, hydromorphone, and morphine may be used multiply for qualitative as well as quantitative determinations of opioids in biologic fluids.

WAINER, B.H., FITCH, F.W., FRIED, J. and ROTHBERG, R.M. A measurement of the specificities of antibodies to morphine-6-succinyl-BSA by competitive inhibition of ^{14}C-morphine binding. Journal of Immunology 110(3): 667-673 (March, 1973)

For abstract, see Section I. Methodology of Drug Research.

WAINER, B.H., FITCH, F.W., ROTHBERG, R.M. and FRIED, J. The structure of morphine monohemisuccinate. Science 178: 647 (November, 1972)

WALSH, C.T., LEVINE, R.R., SQUIRES, C. and TALEVIA, L. Kinetics of C^{14}-methadone absorption from the rat cut and the influence of some physiologic and pharmacologic factors on the absorptive process. Federation Proceedings (in press)

Absorption of C^{14}-methadone as a function of both dose and time was studied in vivo using the closed segment technique. Disappearance of methadone from duodenal segments followed first-order kinetics, consistent with a mechanism of passive diffusion. The half-life of duodenal absorption was 15.6 min with similar values obtained for the jejunum, ileum and cecum. In contrast, the half-life of absorption from the stomach was 10 hr. After gastric intubation of 100 mu-g of methadone, the disappearance of radioactivity from the stomach also followed first-order kinetics with a half-life of 2.1 hr; stomach emptying is therefore the rate-limiting factor in the absorption of methadone. To determine the extent of absorption of orally administered methadone, urinary excretion of radioactivity after administration of a 5 mg/kg dose of C^{14} methadone by gastric intubation was compared with that after s.c. injection. The cumulative urinary excretion of radioactivity in 72 hr was 10.0 ± 3.9% after oral and 15.2 ± 2.4% after parenteral administration, indicating 65.8% absorption by the oral route. Absorption from duodenal segments and disappearance from the stomach following intubation were not affected by 20-day s.c. pretreatment with methadone (5 mg/kg to 10 mg/kg, b.i.d.).

WALSH, M.J., DAVIS, V.E. and YAMANAKA, Y. Tetrahydropapaveroline: An alkaloid metabolite of dopamine in vitro. The Journal of Pharmacology and Experimental Therapeutics 174(3): 388-400 (1970)

Tetrahydropapaveroline (THP) has been found to be a quantitatively important metabolic product of dopamine-C^{14} in rat brainstem and liver homogenates. Methods have been developed for the separation and isolation of THP from tissue extracts. The identity of THP as a metabolite of dopamine in tissue homogenates has been confirmed by thin layer and gas-liquid chromatography and by infrared spectrophotometry. The relative formation of THP in vitro was greatly dependent upon the substrate concentration and upon the amount of nicotinamide adenine dinucleotide available for further oxidation of 3,4-dihydroxyphenylacetaldehyde to 3, 4-dihydroxyphenylacetic acid. THP was the major metabolite of dopamine in the absence of exogenous coenzymes with both liver orbrainstem homogenates. Incorporation of nicotinamide adenine dinucleotide or reduced nicotinamide adenine dinucleotide into incubation mixtures of liver homogenates essentially abolished THP production and markedly enhanced the formation of the acid or neutral metabolites. However, THP remained the major catabolite of the intermediate aldehyde in brain under all conditions. Consequently, the relative amount of dopamine diverted to THP assumed appreciable importance under conditions limiting the oxidation or reduction of 3,4-dihydroxyphenylacetaldehyde. Since THP is known to be pharmacologically active, formation of this alkaloid may be of functional importance.

WAY, E.L., Brain neurohormones in morphine tolerance and dependence. Pharmacology and the Future of Man. Proceedings of the 5th International Congress on Pharmacology, Vol. I. San Francisco, California: Karger, Basel, 1973. Pp. 77-94.

WAY, E.L., HO, I.K. and LOH, H.H. Brain 5-hydroxytryptamine and cyclic AMP in morphine tolerance and dependence. Advances in Biochemical Psychopharmacology Vol. 10. Edited by E. Costa, G.L. Gessa and M. Sandler. New York: Raven Press, 1974. Pp. 219-229.

WAY, E.L. and SETTLE, A. Cholinergic-dopaminergic interaction during morphine abstinence. Presented at the 9th International Congress on Neuropsychopharmacology, Paris, France, July, 1974.

WEI, E., LOH, H.H. and WAY, E.L. Brain sites of precipitated abstinence in morphine-dependent rats. The Journal of Pharmacology and Experimental Therapeutics 185 (1): 108-115 (1973)

The brains of morphine-dependent rats were explored for areas sensitive to naloxone-precipitated withdrawal. Stainless-steel guide cannulas were implanted into different brain areas of male albino rats. One to five days after cannula implantation, physical dependence on morphine was induced by s.c. implantation of a pellet containing 75 mg of morphine base. Naloxone hydrochloride crystals were intracerebraily applied 70 to 76 hours after morphine pellet implantation. After application of naloxone, the abstinence signs of wet shakes and escape behavior were most frequently elicited in the medial thalamus and in medial areas of the diencephalic mesencephalic junctures. Neocortical, hippocampal. hypothalamic, tegmental, lateral thalamic and striatal areas of the brain were less sensitive to naloxone-precipitated withdrawal. The neuroanatomical pathways related to opioid dependence are discussed.

WILLIAMS, N.W. and CLOUET, D.H. The effect of morphine on the uptake and release of neurotransmitters, by isolated synaptosomes. Proceedings of the Fifth International Congress on Pharmacology, San Francisco. California, 1972. P. 253.

WILSON, H.A., PASTERNAK, G.W. and SNYDER, S.H. Differentiation of opiate agonist and antagonist receptor binding by protein modifying reagents. Nature (in press)

WINTER, B.A. and GOLDSTEIN, A. A photochemical affinity-labelling reagent for the opiate receptor(s). Molecular Pharmacology 6: 601-611 (1972)

A radioactive analogue of levorphanol. (^{3}H) N-beta-(p-azidophenyl) ethylnorlevorphanol compound (6), has been synthesized as a photochemical affinity label for the opiate receptor site(s). It has potent opiate-like pharmacological activity in whole mice and isolated intact guinea pig ileum. Upon photolysis of the analogue in the presence of bovine serum albumin as a test protein. radioactivity is incorporated into the protein. Photolysis of the analogue in the presence of total particulate matter from whole mouse brain results in incorporation of radioactivity into a pellet insoluble in water and organic solvent. This incorporation is significantly but incompletely blocked by both levorphanol and destrorphan. Incorporation into guinea pig ileum longitudinal muscle strips is also observed but is not significantly blocked by levorphanol or dextrorphan. The implications of the results are discussed.

WINTER, J.C. Tolerance to a behavioral effect of lysergic acid diethylamide and cross-tolerance to mescaline in the rat: Absence of a metabolic component. The Journal of Pharmacology and Experimental Therapeutics 178(3): 625-630 (1971)

This investigation examined tolerance to lysergic acid diethylamide (LSD) after the administration of LSD or mescaline in rats responding on a fixed ratio schedule of positive reinforcement. After the requisite conditions were established for the development of tolerance in the behavioral situation, the same schedule of drug administration was applied to untrained animals and the levels of LSD in brain and liver were determined. In this way the metabolic component of tolerance was assessed. Pretreatment with either LSD or mescaline for two days preceding the administration of LSD caused a diminution of the rate-depressant effect of LSD. This demonstration of tolerance to LSD and cross-tolerance to mescaline was in agreement with the results of other workers. Determination of the total amount and concentration of LSD in brain and Liver revealed no significant differences between rats which received LSD for the first time and those pretreated with LSD or mescaline, These results indicate that there is no gross alteration in brain and liver levels of LSD concomitant with the development of tolerance to LSD or cross-tolerance of LSD to mescaline in the particular behavioral task studied.

WURSCH, M.S., OTIS, L.S., GREEN, D.E. and FORREST, I.S. ^{3}H-delta-9-THC metabolism in rhesus and squirrel monkeys. Proceedings of the Western Pharmacological Society 15:68 (1972)

Our study was designed to find a suitable primate model for in vivo metabolism of delta-9-THC on which the biotransformations could be studied and suitable methodology for the assay of its metabolites could be developed.

YAGEN, B. and MECHOULAM. R. Stereospecific cyclizations and isomerizations of cannabichromene and related cannabinoids. Tetrahedron Letters 60: 5353 (1969)

YARBROUGH, G.G., BUXBAUM, D.M. and SANDERS-BUSH, E. Biogenic amines and narcotic effects: II. Serotonin turnover in the rat following acute and chronic morphine administration. The Journal of Pharmacology and Experimental Therapeutics (in press)

YARYURA-TOBIAS. J.A., DIAMOND, B. and MERLIS, S. Psychiatric manifestations of levodopa. Canadian Psychiatric Association Journal 17: SS-123 - SS-128 (1972)

YARYURA-TOBIAS, J.A., DIAMOND, B., and MERLIS, S. The action of L-dopa on schizophrenic patients (a preliminary report). Current Therapeutic Research 12(8): 528-531 (August, 1970)

YARYURA-TOBIAS, J.A.. WOLPERT, A., WHITE, L, AGOLA, P. and MERLIS. S. A clinical evaluation of clopenthixol. Current Therapeutic Research 12(5): 271-279 (May, 1970)

YEH. S.Y. and MITCHELL, C.L. Effect of monoamine oxidase inhibitors on formation of morphine glucuronide. Biochemical Pharmacology 21: 571-578 (1972)

The inhibition of the formation of morphine glucuronide in vitro by five monoamine oxidase inhibitors is described. Pargyline and phenelzine at 1.0 and 5.0 X 10^{-4}M concentration and tranylcypromine at 5 and 10X 10^{-4}M concentration were competitive inhibitors of morphine glucuronidation, while isocarboxazide was a mixed-type inhibitor. Nialamide, in the concentrations studied, did not significantly inhibit the formation of morphine glucuronide.

YOUNG, A.B. and SNYDER, S.H. A sensitive specific enzymatic-fluorometric assay for homocarnosine. Journal of Neurochemistry 21: 387-396 (1973)

We have developed a sensitive and specific assay for homocarnosine in tissues. Homocarnosine is separated from GABA by ion exchange chromatography. After hydrolysis of homocarnosine with swine kidney carnosinase, the evolved GABA is measured by an enzymatic-fluorometric procedure. As little as 0.1 nmol of tissue homocarnosine can be detected by this procedure. Homoanserine, which would be detected by this assay, can be separated from homocarnosine by thin layer chromatography. No homoanserine could be detected in any tissue examined. There are marked regional variations in levels of homocarnosine in guinea-pig brain that do not correspond to regional differences in GABA levels.

YU, J.H. and SMITH, C.B. Noncompetitive inhibition by cocaine of uptake and binding of ^{3}H-serotonin by rat brain slices. Presented at the Fifth International Congress on Pharmacology, San Francisco, California, July 23-28, 1972.

ZIMMERMANN, E., GISPEN, W.H., MARKS, B.H. and de WIED, D., editors. Drug Effects on Neuroendocrine Regulation. Progress in Brain Research, Vol. 39. New York: American Elsevier Publishing Company, Inc., 1973.

ZITKO, B.A., HOWES, J.F., RAZDAN, R.K., DALZELL. B.C., DALZELL, H.C., SHEEHAN, J.C., PARS, H.G., DEWEY, W.L. and HARRIS, L.S. Water soluble derivatives of delta-1-tetrahydrocannabinol. Science 177: 442-444 (1972)

Delta-1-tetrahydrocannabinol, which is resinous and insoluble in water and therefore difficult to study pharmacologically, can be converted to a water soluble derivative without loss of its biological activity. This has been achieved by preparing esters bearing a nitrogen moiety with the use of carbodiimide as a condensing agent. The availability of such water-soluble derivatives will allow the evaluation of delta-1-tetrahydrocannabinol in self-administration studies in monkeys for its addiction liability potential in man. This technique of water solubization is also applicable to other compounds of chemical and biological significance.

III

Mechanisms of Action of Different Drugs

III. Mechanisms of Action of Different Drugs

ABEL, E.L., editor. Behavioral and Social Effects of Marijuana. New York: MSS Information Corporation, 1973.

For abstract, see Section II. Drug Chemistry and Metabolism.

ABEL, E.L., McMILLAN, D. E. and HARRIS, L.S. Tolerance to the behavioral and hypothermic effects of 1-delta-9-tetrahydrocannabinol in neonatal chicks. Experientia 28: 1188-1189 (1972)

The development of tolerance to the behavioral effects of marihuana and to its principle active ingredient, 1-delta-9-tetrahydrocannabinol (delta-9-THC) has been demonstrated in various species of adult animals including rats, mice, pigeons, and monkeys. Our experiments with chicks show that tolerance develops not only to the behavioral effects of delta-9-THC but to its physiological effects as well, and that this is also observable in neonatal animals.

ABEL, E.L., McMILLAN, D.E. and HARRIS, L.S. Tolerance to. the hypothermic effects of delta-9-THC as a function of age in the chicken. British Journal of Pharmacology (in press)

ADAMS, M.D., DEWEY, W.L. and HARRIS, L.S. Cardiovascular effects of delta-8- and delta-9-tetrahydrocannabinol in rats. The Pharmacologist 44: 394 (1974)

Intravenous administration (0.1-3.0 mg/kg) of delta-8- or delta-9-tetrahydrocannabinol (THC; solubilized in a mixture of polyoxyethylated vegetable oil, ethanol and saline) produced transient increases in blood pressure in rats followed by a sustained bradycardia and decrease in blood pressure. Tachyphylaxis to the depressor phase limited the number of injections that could be administered to a single animal. Intraarterial injections of delta-8- and delta-S-THC (0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg and 3.0 mg/kg) produced vasoconstriction in the perfused hindquarters of rats. Dose-response curves indicate that delta-8- and delta-9-THC have equal potency with regard to this vasoconstrictor action. No tachyphylaxis to the vasoconstrictor effect was observed. The hindquarter vasoconstrictor response to delta-9-THC (0.3 mg/kg, or 1.0 mg/kg) was not altered by treatment with phenoxybenzamine 100 mu-g/kg). Constrictor responses to delta-S-THC (0.1 mg/kg, 0.3 mg/kg and 1.0 mg/kg) were also measured before and after

phentolamine (1.0 mg/kg). Phentolamine caused slight reductions in responses to 0.1 mg/kg and 0.3 mg/kg delta-9-THC and a significant reduction in response to 1.0 mg/kg delta-9-THC. These data illustrate that delta-8- and delta-9-THC may have vasoconstrictor actions in certain vascular beds which may be independent of stimulation of alpha adrenergic receptors.

ADAMS, W. J., LORENS, S.A. and MITCHELL, C.L. Morphine enhances hypothalamic self-administration in the rat. Proceedings of the Society for Experimental Biology and Medicine 140: 770-771 (1972)

Morphine sulfate (10 mg/kg subcutaneously) suppressed self-stimulation 1-2 hr after injection but augmented it 5-6 hr postadministration. Complete tolerance to the depressant effect was developed after three daily injections. The excitatory effect, however, tended to increase throughout the 5 day testing period.

ADLER, M. W., BENDOTTI, L., GHEZZI, D., SAMANIN, R. and VALZELLI, L. Dependence to morphine in differentially housed rats. Psychopharmacologia (in press)

ADLER, M. W., KOSTOWSKI, W., RECCHIA, V. and SAMANIN. R. Anatomical specificity as the critical determinant of the effect of raphe lesions on morphine analgesia. European Journal of Pharmacology (in press)

ADLEP, M.W., LIN, C., SMITH, K.P., TRESKY, R. and GILDENBERG,. P.L. Lowered seizure threshold as a part of the narcotic abstinence syndrome in rats. Psychopharmacologia 35: 243-247 (1974)

For abstract, see Section I. Methodology of Drug Research.

AGHAJANIAN, G. K. LSD and CNS transmission. Annual Review of Pharmacology 12: 157 (1972)

The research conducted on the effects of D-lysergic acid diethylamide (LSD) and CNS transmission is reviewed to determine its mode and site of action. Much evidence exists to support the assumption that LSD produces its effects by altering synaptic transmission. Moreover, the fact that serotonin containing neurons of the raphe nuclei are selectively sensitive to small parenteral doses of LSD suggests that the drug has its primary effects on specific neurons and synapses linked to the raphe neuronal system rather than on synaptic transmission in general. It is thought that LSD either blocks or mimics serotonin, and there is evidence to support both modes of action. Two-brom-LSD is a potent blocker of serotonin, more so than LSD; however, it has little psychotomimetic activity. On the other hand, LSD but not 2-brom-LSD tends to have a selrotonin like effect at low doses and is inhibitory only at high doses. In any event, the elucidation of the mechanism of action of LSD will require more than isolated obdsertrations on the effects of LSD or serotonin on raphe or other individual neurons. Ultimately it will be necessary to integrate data from the unit level with knowledge about the interconnections and physiological role of the neuronal systems within which these units function.

AGHAJANIAN, G.K. and BUNNEY, B.S. Central dopaminergic neurons: Neurophysiological identification and responses to drugs. Frontiers in Catecholamine Research. Edited by E. Usdin and S.H; Snyder. New York: Pergamon Press, 1973. Pp. 643-648.

For abstract, see Section I. Methodology of Drug Research.

AGHAJANIAN, G.K., BUNNEY, B.S. and KUHAR, M.J. Use of single unit recording in correlating transmitter turnover with impulse flow in monoamine neurons. New Concepts in Neurotransmitter Regulation. Edited by A. J. Mandell. New York: Plenum Press, 1973.

The rate of firing of monoaminergic neurons was recorded to investigate the relationship between monoamine turnover and impulse flow within monoaminergic systems. Recordings from 5-hydroxytryptamine (5-HT) and catecholamine (CA) containing neurons indicate 2 mechanisms of action. One involves a direct effect on monoamine synthesis or degradation in which the rate of firing of monoamine neurons is secondary to the biochemical changes. The second mechanism involves a metabolic change which is secondary to an effect on neuronal firing rate. Mechanisms for other drugs tested are also discussed.

AGHAJANIAN, G.K. and FREEDMAN, D.X. Biochemical and morphological aspects of LSD pharmacology. Psychopharmacology: A Review of Progress, 1957-1967. Edited by D. Efron, J. Cole, J. Levine and J.R. Wittenborn. Washington. D.C. U.S. Government Printing Office, 1968. Pp. 1185-1193.

For abstract, see Section II. Drug Chemistry and Metabolism.

AGHAJANIAN, G. K., HAIGLER, H.J. and BLOOM, F.E. Lysergic acid diethylamide and serotonin: Direction actions on serotonin-containing neurons in rat brain. Life Sciences 11(13): 615-622 (1972)

A study was made of the effects of lysergic acid diethylamide (LSD) and serotonin (5HT) on serotonin-containing neurons in rat brain. LSD and 5HT were applied directly by microiontophoresis to 5HT-containing neurons in the midbrain raphe nuclei. The firing of these neurons was markedly inhibited by both LSD and 5HT. The effects of LSD given systematically and microionophoretically were similar. This suggests that the inhibition of raphe neurons which occurs after the systemic administration of LSD could be due to a direct action of the drug.

ALPERT, M., ANGRIST, B., DIAMOND, F. and FRIEDHOFF, A.J. Effects of high doses of amphetamine on digital tremor in volunteers pretreated with agents which alter biogenic amines. Committee on the Problems of Drug. Dependence. Washington, D.C.: National Academy of Sciences, National Research Council, 1971.

In biochemical studies these workers found that the 1 and d stereoisomers of amphetamine are differentially effective in inhibiting catecholamine uptake into striatal and hypothalamic synaptosoines. Using ^{3}H-dopamine and tissue derived from rat corpus striatum it was found that d and 1 amphetamine were equally effective in blocking uptake. Using ^{3}H norepinephrine and tissue derived from rat hypothalamus it was found that d-amphetamine was ten times more potent in preventing uptake of norepinephrine than l-amphetamine.

ALTSHULER, H. L. and BURCH, N.R. The electroencephalographic effects of cocaine and d-amphetamine in the rhesus monkey as described by period analysis. Proceedings of the Society for Neurosciences 3: 343 (1973)

The electroencephalographic (EEG) descriptors of cocaine are poorly characterized and their mechanisms poorly understood. The effects of cocaine and d-amphetamine on the period analytic descriptors of the electroencephalogram of the monkey, Macaca mulatta, were evaluated when the animal was seated in a primate chair. Each animal served as his own control, and control studies were performed using intravenous (IV) saline injections. IV doses of cocaine (0.05-5.0 mg/kg) and d-amphetamine (0.05-5.0 mg/kg) were administered to each animal in accordance with a randomized experimental design and the EEG continuously recorded for 2 hours after each dose. Periods of photic stimulation (3-30 Hz) were interspersed with periods of spontaneous EEG. A number of changes were observed in the period analytic descriptors. The major period (zero crossings) count was dramatically increased for 5 or more min post-dose. Intermediate period (first derivative) and minor period (second derivative) counts were more variable in their changes, although differences between the drugs were seen at all points of the dose-response curve, in most frequency bands and in responses to photic driving. Reserpine (0.5 mg/kg/day) and 1 DOPA (100 mg/kg/day) were administered chronically to naive monkeys and those previously studied, and the acute effects of cocaine and d-amphetamine evaluated electrographically. Differences in the acute responses to the stimulants were seen in the pretreated animals when compared to the non-pretreated ones. These results implicate central biogenic amines in the actions of d-amphetamine and cocaine on the EEG.

ALTSHULER, H.L., and BURCH, N.R. Period analysis of the electroencephalogram of subhuman primates. Behavior and Brain Electrical Activity. Edited by N.R. Burch and H. L. Altshuler. New York: Plenum Press, 1974.

For abstract, see Section I. Methodology of Drug Research.

A LTSHULER, H.L., BURCH, N.R. and DOSSETT, R.G. The effects of cocaine and d-amphetamine on the spontaneous and photically driven occipital electroencephalogram of the monkey. Federation Proceedings 33(3): 293 (March, 1974)

Some aspects of the mechanisms of central stimulation by cocaine (C) and d-amphetamine (A) were examined. The spontaneous and photically-driven (3-30 Hz) EEG of 3.5-6 kg M. mulatta monkeys was analyzed by period analysis. This technique provides the major period (MAP, baseline cross count), intermediate period (IMP, first derivative) and minor period (MIP, second derivative) descriptors of the spontaneous EEG, and pre- and post-stimulus descriptors of the photically-driven EEG. The occipital area was most effected by both drugs. Following C spontaneous MAP counts change only slightly, while IMP and MIP counts increase dramatically. All three occipital area period descriptors increase following A. The photically-driven EEG was profoundly altered by both drugs, especially shifts in dominant driving frequencies. These alterations, as well as spontaneous changes, were modified by chronic daily treatment with reserpine (0. 5 mg/kg) or l-DOPA (100 mg/kg). Data obtained from parallel experiments without interspersed photic driving suggest that photic stimulation may contribute to the changes seen in the spontaneous, non-stimulated, occipital EEG. The central amine manipulations in this study demonstrate the key role of the biogenic amines in the electrophysiological effects of C and A.

ALTSHULER, H.L., BURCH, N.R.. PHILLIPS, P.E. and DOSSETT, R.G. The effects of cocaine and d-amphetamine on simian electroencephalographic responses to photic driving. Proceedings of the Society for Neurosciences 4: 117 (1974)

Cocaine (C) and d-amphetamine (A) were previously demonstrated to produce pronounced changes in the period analytic descriptors of the spontaneous occipital electroencephalogram (EEG) of the monkey, which were unrelated to photic responses. The current study reports EEG responses to photic stimulation at frequencies of 3-30 Hz following C and A. Experiments were done in which intravenous doses of saline, C (0.5 mg/kg - 5.0 mg/kg) and A (0.25 mg/kg - 2.5 mg/kg) were administered to rhesus monkeys during 90 minute experiments composed of both spontaneous and photically driven EEG recordings. Both drugs caused profound changes in the EEG responses to photic stimulation. Photic driving responses were uniformly inhibited at the stimulation frequency following 2.5 mg/kg of C and 0.5 mg/kg of A, but the responses were shifted to other frequencies often in proximity to the driving frequency. The shift in response frequency was not observed. as shifts to harmonic frequencies, nor were there clear dose-related aspects to the response shifts. The extreme potency of these compounds in altering EEG responses to photic stimulation demonstrates further the profound effects of C and A on the primate visual system.

AMAROSE, A.P., SCHUSTER, C.R. and MULLER, T.P. An animal model for the evaluation of drug induced chromosome damage. Oncology 27: 550-562 (1973)

Cytogenetic analyses of cells subjected to psychotropic drugs are important but restrictive when man is the study subject. An experimental animal system, using the rabbit, was established to ascertain whether a relationship exists between in vivo administration of drugs of abuse and chromosome damage. This report describes the cytogenetic data after acute and/or chronic intravenous administration of d-methamphetamine-HCl, LSD-25, and mitomycin C. The hyperthermia data of LSD-25 were analyzed during the experiments with this drug. A positive control was established with mitomycin C and sterile injectable saline was used for the negative controls. Pre and post chromosome complements failed to show any statistical association between chromosome damage and LSD or methamphetamine. The hyperthermia engendered after the injection of LSD was statistically significant and residual in nature.

ANDERSON, T. and SCHANBERG, S.M. Effect of thyroxine and cortisol on brain ornithine decarboxylase activity and swimming behavior in developing rat. Biochemical Pharmacology (in press)

ANDERSON, T.R. and SLOTKIN, T. Effects of morphine on the rat adrenal medulla. Biochemical Pharmacology (in press)

ANDERSON, T.R. and SLOTKIN, T.A. Maturation of the adrenal medulla - IV. Effects of morphine. Biochemical Pharmacology (in press)

Chronic morphine administration in adult rats results in neurogenic secretion of adrenal catecholamines and compensatory 'increases in basal catecholamine levels, in activities of catecholamine biosynthetic enzymes (tyrosine hydroxylase and dopamine beta-hydroxylase) and in the number of storage vesicles in the tissue. Perinatally addicted developing rats demonstrated changes completely different from those seen in adults: catecholamine levels and dopamine beta-hydroxylase activity were reduced compared to controls and no induction of tyrosine hydroxylase was observed. The time course of adrenomedullary maturation was delayed through the first 10-20 days of age, with reduced numbers of storage vesicles and larger proportions of partially filled vesicles. On exposure to morphine, continued until weaning, perinatally addicted rats did not display any of the changes in catecholamine synthesis or vesicular uptake seen in adult rats. Developing rats treated only in utero or only postnatally demonstrated different types of biochemical deficits which appeared at different times during development. The effects of morphine in developing rats vs. adult rats can be partly explained by the absence of functional innervation of the neonatal adrenal medulla; however other factors may also operate.

ARNFRED, T. and RANDRUP. A. Cholinergic mechanism in brain inhibiting amphetamine-induced stereotyped behaviour. Acta Pharmacologia et Toxicologia 26: 384-394 (1968)

In previous papers we have presented evidence indicating that amphetamine produces stereotyped behaviour continuous sniffing-licking-biting in rats) by activating a dopaminergic mechanism in the corpus striatum (RANDRUP & MUNKVAD 1968. review). This view, however, does not exclude the possibility, that the stereotyped behaviour can be influenced 'inhibited or enhanced) by other transmitter systems in the brain, and published evidence shows that it is prolonged when amphetamine is combined with anticholinergic drugs (SCHELKUNOV 1964).

Thus it is possible that there is a cholinergic mechanism or system in the brain, which antagonizes the stereotyped behaviour. This possibility has been investigated by experiments reported in the present paper,

ASTON, R. Mechanisms contributing to barbiturate intolerance in rats. British Journal of Pharmacology 49: 527 (1973)

Female rats, 3 weeks after pretreatment with 200 or 400 (mg/kg)/ day barbitone for 2 or 30 days, exhibited a prolonged sleeping time and a reduced awakening barbiturate brain level when challenged with either barbitone or pentobarbitone. After 3 additional weeks, the latter responses had returned, or were returning to, control values.

Barbitone pretreatment schedules had no residual effect upon in vitro hepatic pentobarbitone-metabolizing activity measured 3 or 6 weeks later, except in one instance, when hepatic enzyme activity was significantly enhanced 3 weeks after 30 daily doses of 200 mg/kg barbitone. In this case, however, an enhanced barbiturate sleeping time, together with a reduced awakening barbiturate brain level, were observed.

Aston, R. continued

It is concluded that barbitone administered intraperitoneally in doses of 200 to 400 (mg/kg)/day for 2 or 30 days induces a non-hepatogenic intolerance to barbiturates, related to an increased sensitivity of the central nervous system to these drugs. This central intolerance is seen 3 weeks, but not 6 weeks, after pretreatment. Furthermore, this central intolernace has been observed to co-exist with an hepatic tolerance, a situation which could result in a reduced LD_{50} coupled with an increase in ED_{50}.

ASTON, R. and HIBBELN, P. Induced hypersensitivity to barbital in the female rat. Science 157(3795): 1463-1464 (September, 1967)

Female rats, treated with two daily anesthetic doses of barbital, exhibit 1 month later a significant increase in sleeping time over that of control animals. Hypersensitive animals, as compared to controls, show no alteration in liver weight (as percentage of body weight), but they manifest a significant shortening of time for induction of anesthesia. Induced hypersensitivity to barbiturates is apparently not the result of alterations in the metabolism of these agents, but it may be related to enhanced susceptibility of the central nervous system to these drugs.

AYHAN, I.H. Daily susceptibility variations. to the morphine-induced hyperactivity of rats. Journal of Pharmacy and Pharmacology 26: 76-78 (1974)

AYHAN, I.H. and RANDRUP, A. Inhibitory effects of amphetamine, L-DOPA and apomorphine on morphine-induced behavioural excitation of rats. Archives internationales de Pharmacodynamie et de Therapie 204(2): 283-292 (August, 1973)

The influence of amphetamine, L-DOPA and apomorphine on morphine-induced hyperactivity was studied in rats. A small dose of morphine (2 mg/kg) produced stimulation of locomotion, rearing and grooming. By combined administration, amphetamine, L-DOPA and apomorphine potentiated each other with respect to behavioural effects. In contrast, these three drugs strongly inhibited the occurrence of morphine-induced behavioural excitation. These results support the idea that the mechanism of morphine-induced hyperactivity differs from that of amphetamine, L-DOPA and apomorphine and stimulation of rats' behaviour by morphine is probably not due to the activation of. dopaminergic systems in the brain.

AYHAN, I.H. and RANDRUP, A. Role of brain noradrenaline in morphine-induced stereotyped behavior. Psychopharmacologia 27: 203-212 (1972)

The injections of morphine into rats which had been made tolerant to morphine produced stereotyped sniffing, licking and biting reminiscent of amphetamine-stereotypy. Pretreatment with drugs acting on the brain catecholamines such as reserpine, H 44/68. FLA-63 and receptor blockers could inhibit this behaviour. Comparison between morphine and amphetamine stereotypy indicated that brain noradrenaline plays a more important role than dopamine in morphine induced stereotyped behaviour, in contrast to amphetamine stereotypy where dopamine is the most important brain amine. The result of experiments with intraventricular injections of noradrenaline supported this conclusion. because the noradrenaline suppressed the blocking action of FLA-63 on morphine-induced stereotypy.

BABBINI, M. and DAVIS, W.M. Time-dose relationships for locomotor activity effects of morphine after acute or repeated treatment. British Journal of Pharmacology 46(2): 213 (October, 1972)

Effects of morphine sulphate (1.25, 2.5, 5, 10, 20 and 40 mg/kg i. p.) on locomotor activity of male rats were observed for 8 h after single doses in non-tolerant rats. The lower three doses had only an excitatory effect, whereas the higher three doses caused initial depression followed by a delayed excitatory effect.

The same doses of morphine were administered daily for 30 days. No tolerance developed within this time to the excitatory effect. The locomotor excitatory effect of the higher three doses of morphine became progressively more pronounced over treatment periods of 30 days (and 48 days for 20 mg/kg), while the latency to peak activity decreased.

An explanation of these results is suggested on the basis of two different central drug-receptor interactions affecting motility.

BAILEY, D.N. and JATLOW, P.I. Chemical analysis of massive crystalluria following primidone overdose. American Journal of Clinical Pathology 58(5): 583-589 (November, 1972)

For abstract, see Section II. Drug Chemistry and Metabolism,

BAKER, W.W. Excitatory responses following intracaudate injection of N-methyl-dl-aspartic acid. Archives internationales de Pharmacodynamie et de Therapie 196: 226-234 (1972)

In chronic cats, unanesthetized and anesthetized, intracaudate microinjections of N-methyl-dl-aspartic acid (NMA) produced a broad spectrum of excitatory responses which included: rage (only unanesthetized preparation), tremors and gross body movements, mydriasis and salivation. 'In the anesthetized preparations, intracaudate NMA also exerted an analeptic action in that it activated the cortex (abolished spindling activity), roused the animal with opening of eyelids, involuntary movements. vocalization. increased respiration and accelerated heart rate. These actions were transient and the animal lapsed back into an anesthetic state. However, upon supplemental injections of NMA analeptic effects were repeatable without any evidence of cumulative action or tachyphylaxis. Caudate-mediated NMA excitatory responses were not blocked by pretreatment with either local scopolamine (in contrast to carbachol) or tetracaine. It is concluded that the caudate participates directly in modulating motor, behavioral and electrocortical activities, and that the depolarizing action of local NMA disrupts inhibitory control in the caudate to produce extensive excitation of the C.N.S.

BAKER, W.W. and BENEDICT, F. Analysis of local discharges induced by intrahippocampal microinjection of carbachol or diisopropylfluorophosphate (DFP). International Journal of Neuropharmacology 7: 135 -147 (1968)

Following intrahippocampal injections, carbachol and diisopropylfluorophosphate (DFP) each were highly effective in producing hippocampal discharges; electrographically, both types of discharges resembled one another. Our data indicate that these discharges are both of cholinergic origin and result from an action on local "muscarinic" receptors. However, the build-up and persistence of endogenously released acetylcholine precede the DFP discharges. These cholinergic discharges were readily suppressed by intrahippocampal scopolamine, a potent muscarinic antagonist. In contrast, nicotinic blocking agents were ineffective. This coupled with the unresponsiveness of the hippocampus to nicotine and pharmacologically related agonists strongly suggests an absence of "nicotinic" receptors in this area. Of the other antagonists, tetracaine was almost as effective as scopolamine in abolishing cholinergic discharges: whereas, pyridine-2-aldoxime methiodide (2-PAM) was specific only against the DFP discharges since it reversed in situ the inhibition of cholinesterase by DFP. Antagonism of carbachol effects by 2-PAM was negligible. It appears that the levels of acetylcholine and its actions on "muscarinic" receptors are critical in influencing hippocampal function. These local cholinergic systems in the hippocampus might then be expected to assume special significance in normal and abnormal brain activities.

BAKER, W.W. and BENEDICT, F. Differential responses of hippocampal repetitive discharges to scopolamine and pentobarbital. Experimental Neurology 21: 187-200 (1968)

The hippocampus responded to microinjected drugs by producing two' well-defined patterns of repetitive activities, firing either intermittently or continuously. The intermittent discharges, established after intrahippocampal picrotoxin or d-tubocurarine (dTC), developed as discrete foci which fired cyclically as spike-waves with an interposed afterdischarge; the continuous discharges, established after microinjected carbachol or diisopropylfluorophosphate (DFP), fired as sustained, uninterrupted spikes of uniform amplitude. These patterned discharges were further contrasted by their differential susceptibilities to intravenous pentobarbital or scopolamine. The afterdischarge components of both the dTC and picrotoxin foci were differentially suppressed by small doses of pentobarbital (1-5 mg/kg); whereas, the continuous discharge activity due to either carbachol or DFP, was selectively abolished by scopolamine (0.1 mg/kg). The afterdischarges eliminated by pentobarbital were readily restored, but the cholinergic discharges abolished by scopolamine were difficult to reestablish, Significantly, both the spike-wave of the foci and the uninterrupted spike discharges were considerably more resistant to pentobarbital. According to our interpretations, the afterdischarges are related to lowering of presynaptic inhibition which pentobarbital antagonizes by either directly or indirectly increasing local inhibition, thus raising the local threshold of excitability. By contrast, the continuous discharges are attributed to actions at presynaptic and postsynaptic cholinergic receptors; scopolamine is more effective against this activity by virtue of its direct and selective interference with these local cholinergic excitatory mechanisms. Our findings call attention to some of the critical interactions of local excitatory and inhibitory processes in the hippocampus, and demonstrate their importance not only in generating local discharges, but also in the patterning of the type of repetitive activity.

BAKER, W.W. and BENEDICT, F. Increased local cholinergic activity on hippocampal foci. Federation Proceedings 28: 775 (1969)

Hippocampal foci each with a characteristic pattern of firing were developed acutely in cats by microinjecting focogenic agents intrahippocampally (I.H.). Cholinergic activity was increased at the focus site by supplementary microinjections of carbachol or an anticholinesterase. Carbachol (5 mu-g I.H.) stimulated foci with increased firing rates. lengthened afterdischarges and intermittent seizures. These effects were antagonized by I. H. scopolamine (10-30 mu-g). Initially, diisopropylfluorophosphate (DFP) and physostigmine accelerated firing rates of foci but then markedly depressed their excitability. Depressed activity, however, was restored by small doses of I. H. acetylcholine (ACh). Excitation by neostigmine paralleled that by carbachol. Because of their quaternary structure and limited lipid solubilities, excitation by carbachol and neostigmine are attributed to actions on superficial cholinergic sites. Inhibition by DFP and physostigmine (build-up of endogenous ACh) are ascribed to actions on less accessible "Interior" ChE stores (and ACh receptors): these sites are bounded by a lipid barrier. Our results suggest a potential role of these local cholinoceptive mechanisms in determining the fate of hippocampal foci.

BAKER, W.W. and BENEDICT, F. Local electrographic responses to intrahippocampal d-tubocurarine and related neuromuscular blocking agents. Proceedings of the Society for Experimental Biology and Medicine 124: 607-611 (1967)

Our research was primarily structured to analyze the local electrographic patterns of excitation induced by dTC microinjected into the hippocampus. To characterize this activity further, the study was expanded to include other neuromuscular blocking agents. We hoped also to characterize the local mechanisms associated with hippocampal effects of dTC and if possible, to relate these to the cholinergic receptor mechanisms which have been defined pharmacologically at the neuromuscular junction.

BAKER, W.W. and BENEDICT, F. Selective effects of i.v. pentobarbital and scopolamine on chemically-induced repetitive discharges in the hippocampus. Federation Proceedings 27:571 (1968)

BAKER, W.W. and CONNOR, J.D. Production of tremor by intracaudate cholinergic agents and its suppression by locally administered catecholamines. Excerpta Medica, International Congress Series, No. 154. Amsterdam, the Netherlands: Excerpta Medica Foundation, 1967. P. 32.

Of a series of cholinergic muscarinic agents microinjected into the caudate nucleus, carbachol (anafog of acetylcholine) was the most potent in producing limb tremors in cats. Tremors similarly developed after intracaudate anticholinesterases which potentiated the acetylcholine released endogenously. In contrast, cholinergic nicotinic agents were totally inactive. Muscarinic blocking agents (belladonna alkaloids), administered locally suppressed carbachol-induced tremors; nicotine blocking agents were ineffective. These findings indicate that cholinergic agents act specifically on "muscarinic" receptors in the caudate to produce involuntary movements.

Baker, W.W. and Connor, J.D. continued

Tremors induced by carbachol were readily suppressed also by intracaudate catecholamines, but not by other sympathomimetics which are non-catecholamines. Antitremor potencies of the catecholamines paralleled their order of beta-receptor activity as defined by Ahlquist. Intracaudate pretreatment with beta-adrenergic blocking drugs, however, prevented this inhibition of cholinergic tremors: locally injected alpha-adrenergic blocking agents under comparable conditions were ineffective. These results coupled with our finding that microinjected adenosine triphosphate (ATP) also abolished tremors suggest that suppression of the carbachol tremors by the catecholamines is mediated by a "metabolic" effect involving beta-adrenergic receptors.

Since in the caudate increased cholinergic activity elicited tremor, whereas the catecholamines suppressed this activity, we feel justified in concluding that the level of these. neurotransmitters are critically balanced and thus participate dynamically in the regulation of involuntary motor activity.

BAKER, W.W., CONNOR, J.D., ROSSI, G.V. and LALLEY, P.M. Production of tremor by intracaudate cholinergic agents and its suppression by locally administered catecholamines. Progress in Neuro-Genetics, Vol, 1. Edited by A. Barbeau and J. R. Brunette. Amsterdam, the Netherlands: Excerpta Medica Foundation, 1969. Pp. 390-403.

Cholinergic agents microinjected into the caudate nucleus produced tremor by a selective and persistent action on local muscarinic acetylcholine receptors. Carbachol (an analog of acetylcholine resistant to hydrolysis by cholinesterase), the most potent of these, acted directly on the receptors. The anticholinesterases, also tremorogenic, exerted their primary effects by inhibiting cholinesterase and thus permitted a piling up of endogenous acetylcholine to interact with the muscarinic receptors. Sustained tremor activity, which required the persistent receptor action of carbachol or acetylcholine was readily abolished by intracaudate injection of muscarinic blocking agents.

Tremor was also suppressed by intracaudate catecholamines, epinephrine and dopamine, and by adenosine triphosphate (ATP). Evidence based on the effectiveness of beta-adrenergic antagonists in blocking this suppression by catecholamines Indicates that this tremor inhibition is mediated specifically by beta-adrenergic receptors in the caudate. Anti-tremor effects of both the catecholamines and ATP are interpreted as linked together in a metabolic schema in which both are capable of accelerating the enzymatic conversion of glycogen to glucose. In this proposal additional glucose is needed to offset the increased requirements associated with the cholinergic mechanisms contributing to tremor.

Our study substantiates a hypothesis that acetylcholine-dopamine levels are critically balanced in the caudate and 'by their action on specific receptors these neurotransmitters comprise an important local tremor regulatory mechanism. The results suggest that reduced cholinesterase functioning also merits attention as a contributory local factor in tremorogenesis.

BAKER W.W. and KRATKY, M. Changes in local excitability produced by intrahippocampal injections of thiosemicarbazide and GABA. Archives internationales de Pharmacodynamie et de Therapie 170: 81-92 (1967)

BAKER. W.W. and KRATKY, M. Differential suppression of spontaneous and evoked hippocampal electrical activities by local tetracaine. Archives internationales de Pharmacodynamie et de Therapie 173: 395-410 (1968)

When microinjected, tetracaine suppressed spontaneous electrical activity as well as various types of locally induced electrical discharges at the hippocampal injection site. The evoked activities anlyzed were representative of local responses of neuronal population in the hippocampus to microinjected drugs and included: 1) sustained cholinergic discharges related to local action of carbachol or diisopropylfluorophosphate, and 2) intermittent focal discharges produced by intrahippocampal d-tubocurarine (dTC). Tetracaine was most effective in abolishing spontaneous background electrogram and the cholinergic discharges, but was significantly less active against dTC spike-wave. After tetracaine suppression, spontaneous and discharge activities could be partially restored with supplemental microinjections of cholinergic agents but not with calcium. Excitability of partially suppressed dTC foci was enhanced by increasing local cholinergic activity. Although the differential suppression of neuronal activity by tetracaine has been meaningfully interpreted as due to a specific interference with local cholinergic mechanisms, other less specific actions also warrant serious consideration. From this emphasis on cholinergic mechanisms, our findings further suggest that the levels of acetylcholine are critical in regulating local excitability in the hippocampus and as such are directly involved in normal and abnormal functioning of this brain area.

BAKER, W.W., ZIVANOVIC, D. and MALSEED, R.T. Contrasting local effects of MAO inhibitors on caudate tremor activities. European Journal of Pharmacology (in press)

BAKER, W.W., ZIVANOVIC, D., MALSEED, R.T. and MAHONEY, R. Differential effects of MAO inhibitors on caudate tremorgenic activity. Federation Proceedings 31: 290 (1972)

Tremor responses were elicited in chronic cats by intracaudate microinjections of the MAO inhibitors tranylcypromine (TRAN) and harmaline (HARM), but not pargyline (PARG). This tremorgenesis may involve alterations in functional levels of monoamines (NE, DA, 5-HT) in the caudate following blockade of their metabolic deamination. Characteristics (latency, amplitude, frequency) of TRAN (160-360 mu-g) and HARM (130-380 mu-g) tremors were similar, differing principally in their duration of tremor (5 days with TRAN; 1 hr with HARM). TRAN tremor appeared to involve cholinergic intervention since it was suppressed by 120 mu-g of hemicholinium (HC-3). an inhibitor of ACh synthesis. Following suppression by HC-3, increased sensitivity to ACh was apparent since tremor activity was transiently re-established at doses of ACh (25 mu-g) usually ineffective in initiating tremor. Conversely, HARM tremor was resistant to suppression by HC-3. Endogenous cholinergic (PHYSO) tremors were readily abolished by local injections of PARG (120-200 mu-g); however, TRAN (200 mu-g) required a substantially longer latency to effect tremor suppression. Our results indicate differential effects of MAO inhibitors on tremorgenic mechanisms in the caudate which we attribute to differences in their ability selectively to inhibit MAO, as well as to alter the balance of neurotransmitters locally.

BANERJEE, S.P., and SNYDER, S.H. Cannabinoids: Influence on neurotransmitter uptake in rat brain synaptosomes. The Journal of Pharmacology and Experimental Therapeutics (in press)

BARRY, H. Classification of drugs according to their discriminable effects in rats. Federation Proceedings 33(7): 1814-1824 (July, 1974)

For abstract, see Section I. Methodology of Drug Research.

BECKER, F., ROSSMAN, T., REISS, B. and SIMON. E.J. The effect of levorphanol tartrate on ribonucleic acid synthesis in normal and regenerating rat liver. Research Communications in Chemical Pathology and Pharmacology 3(1): 105 (1972)

The ability of levorphanol. a synthetic analogue of morphine. to inhibit the synthesis of RNA in normal and regenerating liver has been studied. Hepatocytes were fractionated in a manner which permitted examination of the synthesis of ribosomal and non-ribosomal RNA from the cytoplasm and nucleus. The synthesis of every fraction of RNA of the normal hepatocyte was almost totally inhibited by this agent at the indicated dose. Seventy-percent hepatectomy induced an enormous increase in the synthesis of most of the RNA fractions examined. Levorphanol severely inhibited the synthesis of all ribosomal RNA components in regenerating rat liver. A less severe but significant depression of the synthesis of non-ribosomal components also occurred. These results suggest that levorphanol inhibits the synthesis of all classes of hepatocyte RNA, though the effect is somewhat more pronounced on the synthesis of ribosomal RNA components.

BENNETT, J.L. and AGHAJANIAN. G.K. Stereospecific binding of D-LSD and physiological response to serotonergic neurons. Federation Proceedings 33(3, part I): 256 (1974)

D-lysergic acid diethylamide (D-LSD) in low doses (10 midrograms/kg) inhibits the firing of serotonergic neurons in rat brain: to explore the possibility that this action may be mediated by a high-affinity receptor, the binding of D-LSD to rat brain homogenates was studied. A high-affinity binding site was detected; reduction in binding occurred when homogenates were preheated (80 degrees C) when the incubation was at 4 degrees C instead of 37 degrees C, or when serotonin was present. L-LSD competed with the binding of D-LSD in a low but not high-affinity range, indicating only the latter is stereospecific. High-affinity binding was found in cerebral cortex, striatum, and midbrain, but not in cerebellum. The concentration of D-LSD in brain after I.V. injections which just inhibit serotonergic neurons was in the same range as the above high-affinity binding. L-LSD had no effect on the firing rate of serotonergic neurons even at 100 times the dose of D-LSD. These results suggest a correlation between the physiological action of D-LSD on serotonergic neurons and the high-affinity binding of D-LSD to brain homogenates: both are sterospecific and occur in the same low concentration range.

BEN-ZVI, Z., MECHOULAM, R. and BURSTEIN, S. Identification through synthesis of an active delta-1(6)-tetrahydrocannabinol metabolite. Journal of the American Chemical Society 92: 3468 (1970)

BEN-ZVI, Z., MECHOULAM, R., EDERY, H. and PORATH, G. 6-beta-delta-l-tetrahydrocannabinol. Synthesis and biological activity. Science 174: 951 (1971)

For abstract, see Section II. Drug Chemistry and Metabolism.

BEYER, J.R. and ELLIOTT, H.W. A comparative study of the analgesic and respiratory effects of N-allylnorcodeine (nalodine), nalorphine, codeine and morphine. The Journal of Pharmacology and Experimental Therapeutics (in press)

BHARGAVA, H.N., AFIFI, A-H. and WAY, E.L. Effect of chemical sympathectomy on morphine antinocicgption and tolerance development. Biochemical Pharmacology 22: 2769-2772 (1973)

BHARGAVA, H.N. and WAY, E.L. Brain acetylcholine (ACh) and choline (Ch) changes during acute and chronic morphinization and during abrupt and naloxone precipitated withdrawal in morphine tolerant-dependent mice and rats. Proceedings of the Western Pharmacological Society 17: 173-177 (1974)

BHARGAVA, H.N. and WAY, E.L. Morphine tolerance, dependence and withdrawal and brain acetylcholine (ACh). The Pharmacologist 16(2): 270 (1974)

For abstract, see Section II. Drug Chemistry and Metabolism.

BIANCHINE. J.R. and EADE, N.R. The effect of 5-hydroxytryptamine on the cotton pellet local inflammatory response in the rat. Journal of Experimental Medicine 125: 501-510 (1967)

The cotton pellet technique was used to evaluate the effect of 5-HT and certain related compounds on granuloma formation in the rat. 5-HT (10 mg/kg) significantly decreased granuloma formation, significantly increased adrenal weight, and significantly decreased thymus weight in normal rats, and significantly decreased granuloma formation and thymus weight in sham-operated rats. On the other hand, 5-HT (10 mg/kg) significantly increased granuloma weight in adrenalectomized rats.

Methysergide (1 mg/kg) blocked the inhibitory effect of 5-HT on granuloma formation as well as the changes in weight of adrenal and thymus glands.

5-HIAA (11 mg/kg) and 5-HTP (13 mg/kg) failed to alter granuloma formation.

BICHER, J.L. and MECHOULAM, R. Pharmacological effects of two active constituents of marihuana. Archives internationales de Pharmacodynamie et de Therapie 172: 24-30 (1968)

For abstract, see Section II. Drug Chemistry and Metabolism.

BLUMBERG, J.B., TAYLOR, R.E. and SULSER, F. Modification by antipsychotic drugs of the cyclic 3',5'-AMP (cAMP) response to d-LSD in rat brain following microwave irradiation. Federation Proceedings 32: 496 (1973)

It has previously been reported that d-LSD raises the concentration of AMP in brain and that trifluoperazine prevented this effect (Uzunov and Weiss, Pharmacologist 13, 257, 1971). In the present experiments. amounts of AMP were estimated in discrete areas of the brain after exposure of rats to microwave irradiation to eliminate artifacts produced by decapitation. d-LSD (0.5 mg/kg i.p.) rapidly and significantly increased the concentfatioh of AMP in cortex and midbrain with the maximum increase occurring at 20 minutes (160-20%). No significant increase was noted in cerebellum and brainstem. BOL (0.5-2.0 mg/kg i.p.) was without effect. Chlorpromazine (10 mg/kg i.p.), haloperidol (5 mg/kg i.p.) and pimozide (5 mg/kg i.p.) did not change the basal levels of AMP-in any brain area except the cortex but effectively inhibited the LSD induced increase in AMP in cortex and brainstem. Regardless of the molecular mechanism involved, these and earlier. findings (Palmer et al., Psychopharmacologia 23, 201, 1972) suggest that the AMP system in brain may be implicated in the pharmacological activity of antipsychotic drugs.

BOISSE, N.R. and OKAMOTO, M. Comparison of barbital and pentobarbital physical dependence in the cat. The Pharmacologist 16: 247 (1974)

Despite the failure of long-acting barbiturates to result in severe physical dependence in man, barbital has long been the choice for the experimental production of dependence. To effectively compare the abstinence characteristics of short and long-acting barbiturates, cats were treated 5 weeks with barbital (B) or pentobarbital (P) intra-gastrically in maximally tolerable doses at intervals allowing equi-effective recovery to provide an equiv. chronic CNS depression. Kinetic analysis of blood levels shows the fractional change in blood conc. of B and P to be the same reinforcing treatment equivalency. P abstinence is most severe culminating in a 10% incidence of convulsions and 30% death. In contrast, all cats survived B abstinence and seizures were usually absent. Results of substitution expts, wherein B replaced P or P replaced B following chronic treatment suggest an important role for elimination kinetics ($t_{\frac{1}{2}}$) in abstinence. To exclusively manipulate $t_{\frac{1}{2}}$, a schedule of 1st. -order dose reduction was developed to extend P $t_{\frac{1}{2}}$ to that of B. These findings confirm the important role of $t_{\frac{1}{2}}$ in the overt expression of an underlying dependence. Also, this study permits a comparison of effectiveness of B and P to induce dependence.

BOLT, A.G. and FORREST. I.S. In vivo and in vitro interactions of chlorpromazine and melanin. Chapter 4 of Recent Advances in Biological Psychiatry, Vol. X. New York: Plenum Press, 1968. Pp. 20-28.

For abstract, see Section II. Drug Chemistry and Metabolism.

BONNET, K.A. and ROGERS, J. Regional studies of the consequences of acute and chronic intracerebral morphine injection. Presented at the Fourth Annual Meeting of the Society for Neuroscience, St. Louis, Missouri, October 20-24, 1974.

Fisher rats were implanted with bilateral fine guage cannulae for injection of morphine into discrete brain structures. Footshock sensitivity was determined for four motoric responses and vocalization by a modified jump-flinch procedure. Bilateral injections of saline one week postoperatively revealed significant group differences in shock sensitivity. Bilateral 1 or 10 mu-g morphine injections produced different response category profiles for each implant group. Caudate animals became hypersensitive in most response categories. Center median animals were dramatically analgesic in the vocalisation response. Only substantia nigra animals resembled the response profiles of animals given systemic morphine. Repeated 10 mu-g injections resulted in tolerance on all response categories for substantia nigra, and loss of hyperalgesia in the caudate animals. Posterior hypothalamus showed increasing analgesia with successive injections and no indications of tolerance development. Subsequent systemic morphine injection (5 mg/kg) was reduced in analgesic effects only in animals given repeated morphine injections into the posterior hypothalamus.

BORGEN, L.A. and DAVIS, M. Cannabidiol interaction with delta-9-tetrahydrocannabinol. Research Communications in Chemical Pathology and Pharmacology 7(4): 663 (1974)

Two experiments were conducted in rats and rabbits concerning the effects of cannabidiol (CBD). a supposedly inactive marihuana constituent, on several actions of delta-9-tetrahydrocannabinol (delta-9-THC). In rats, 25 mg/kg of CBD given i.p. 30 min. prior to 10 mg/kg delta-9-THC reduced the magnitude and duration of the hypothermic effects of delta-9-THC, while CBD alone had no effect on body temperature. CBD (25 mg/kg. i.v.) given 1 hr. before delta-9-THC (3 mg/kg, i.v.) to unanesthetized rabbits caused a significant attenuation of the depressant effects of delta-9-THC on heart rate, respiration and rectal temperature. These data suggest that although CBD is relatively inactive compared to delta-9-THC. it may be a potential competitive antagonist of the effects of delta-9-THC.

BORGEN, L.A. and DAVIS, W.M. Cannabidiol (CBD) attenuation of effects of delta-9-THC. The Pharmacologist 15(2): 201 (1973)

Studies were conducted in 3 species concerning the effects of CBD on various actions of delta-9-THC. In the rat and pigeon, CBD pretreatment (25-50 mg/kg, 1 hr. prior) reduced the operant depressant effects of delta-g-THC (1-3 mg/kg) on V160" or F160" schedules of food-reinforced performance. CBD alone had no effect at these dosages. Similarly, CBD (25 mg/kg, i.p.) given prior to 10 mg/kg delta-9-THC reduced both the magnitude and duration of hypothermic effects of delta-9-THC, while having no effect on body temp. when given alone. CBD and delta-9-THC, individually and in combination, were administered i.v. to unanesthetized rabbits equipped for recording of body temp., EKG, and respiration. Delta-9-THC (3 mg/kg), produced a 3.5-4.3°C drop in temp. and a 40-50% drop in heart and respiration rate. effects which were maximal at 2-3 hr. post-injection. CBD (25 mg/kg i.v.) had no effect on body temp., but produced a 10-20% drop in heart and respiration rate which lasted 30-45 min. CBD (25 mg/kg) 1 hr. before delta-9-THC (3 mg/kg) caused an attenuation of delta-9-THC effects on all 3 parameters, both in magnitude and duration. Thus, although CBD is relatively inactive compared to delta-9-THC, it may be a potential competitive antagonist of delta-9-THC effects.

BORGEN, L.A., LOTT, G.C. and DAVIS, W.M. Cannabis-induced hypothermia: ,A dose-effect comparison of crude marihuana extract and synthetic delta-g-tetrahydrocannabinol in male and female rats. Research Communications in Chemical Pathology and Pharmacology 5(3): 621 (May, 1973)

Synthetic delta-9-THC was found to produce a greater hypothermic effect in rats than a crude marihuana extract containing a larger delta-9-THC dosage. Additionally, female rats showed a more pronounced hypothermic response than males to both delta-9-THC and the marihuana extract.

BOWERS, M.B., JR. Acute psychosis induced by psychotomimetic drug abuse. II. Neurochemical findings. Archives of General Psychiatry 27: 440-442 (October, 1972)

For abstract, see Section II. Drug Chemistry and Metabolism.

BOWERS, M.B., JR. Cerebrospinal fluid 5-hydroxyindoleacetic acid (5HIAA) and homovanillic acid (HVA) following probenecid in unipolar depressives treated with amitriptyline. Psychopharmacologia 23: 26-30 (1972)

Lumbar cerebrospinal fluid 5-HIAA, HVA, and the ratio 5-HIAA/HVA were measured followed probenecid administration in eleven patients with unipolar depression before and during treatment with amitriptyline (AMI). Control values were obtained from a group of inmate volunteers. Prior to treatment CSF 5HIAA formation in the depressives was not different from controls. During treatment with AMI, CSF 5-HIAA formation decreased. One patient with psychotic symptoms prior to AMI and two patients who developed psychotic reactions on AMI showed relatively low CSF 5HIAA formation prior to antidepressant therapy. Compared to controls CSF HVA values were higher in the depressives prior to AMI therapy.

BOWERS, M.B., JR. 5-hydroxyindoleacetic acid (5HIAA) and homovanillic acid (HVA) following probenecid in acute psychotic patients treated with phenothiazines. Psychopharmacologia 28: 309-318 (1973)

Lumbar CSF 5HIAA and HVA were measured following probenecid administration in acute psychotic patients before and during treatment with phenothiazines. Patients with more classical schizophrenic symptoms had higher values for 5HIAA/HVA than other psychotics. depressives, and inmate volunteers. Prior to treatment CSF 5HIAA, but not HVA, correlated significantly with several clinical items related to psychotic disorganization. Phenothiazine treatment produced significant increases in CSF HVA which could not be correlated with the dose of antipsychotic or antiparkinson drugs.

BOYD. E.S., BOYD, E.H. and BROWN, L.E. The effects of some drugs on an evoked response sensitive to tetrahydrocannabinols. The Journal of Pharmacology and Experimental Therapeutics 189(3): 748 (1974)

The effects of several drugs were compared with those of delta-g-tetrahydrocannabinol (delta-9-THC) on responses evoked in frontal lobe polysensory areas, ipsi- and contralateral to the stimulus site in primary somatosensory cortex, in squirrel monkeys with postmesencephalic or high spinal sections. Delta-9-THC augmented both the early evoked response and the late evoked response, which occurs 150 to 200 msec after the stimulus. It also frequently augmented or induced repetitive synchronous activity after the late response. In contrast, pentobarbital, ethanol and diethyl ether depressed both early and late responses, while chlorpromazine and chloralose depressed late responses without consistently affecting early responses; none of these drugs induced late repetitive activity. Mescaline had effects similar to those of delta-9-THC on late responses. but its effect on early responses was much less. Lysergic acid diethylamide had little effect on early responses but depressed late responses at high doses. Phencyclidine also had little effect on early responses. It facilitated late responses at low doses and depressed them at high doses. Picrotoxin and pentylenetetrazol had effects similar to, but greater than, those of delta-9-THC. Strychnine had variable, and mostly small, effects on evoked responses. Gallamine, atropine, amphetamine, levarterenol and methoxamine were essentially without effect on the responses studied. It is concluded that the effects of delta-9-THC and mescaline on these responses in polysensory cortex are similar to those of certain convulsants but are unlike those of depressants or of amphetamine, levarterenol, lysergic acid diethylamide, phencyclidine or strychnine.

BOYD, E.S., BOYD, E.H. and BROWN, L.E. Effects of tetrahydrocannabinols on evoked responses in polysensory cortex. Annals of the New York Academy of Sciences 191: 100-127 (1971)

Graded doses of delta-8- and delta-9-THC's were given to the encephale isole squirrel monkey and the effects compared to those of pentobarbital and ethanol on early and late responses evoked in the postarcuate polysensory area. an area of cerebral cortex where sensory integration has been postulated to occur. The early and late responses. which were evoked by stimulation of primary somatosensory cortex, were found to be locally generated at the recording site, to have the same pattern of cortical distribution, and to interact with each other in a complex fashion that included the resetting of the late responses by a second early response. Tetrahydrocannabinols increased the amplitudes of the early responses; low doses of pentobarbital and ethanol had variable effects on them, whereas high doses depressed them. An even more striking differential effect of the THC's was observed on the late responses. They caused a dose-dependent increase in the late responses, followed by rhythmic activity, whereas all doses of pentobarbital and ethanol tested depressed the late responses. It is suggested that these differential effects of THC's may underlie the distortions of sensory perception or of time sense in humans caused by marijuana and THC's, or they may underlie the hyperreactivity to sensory stimuli reported in experimental animals.

BOYD, E.S., BOYD, E.H., MUCHMORE, J.S. and BROWN, L.E. Effects of two tetrahydrocannabinols and of pentobarbital on cortico-cortical evoked responses in the squirrel monkey. The Journal of Pharmacology and Experimental Therapeutics 176: 480 (1970)

The effects of two tetrahydrocannabinols (delta-8-THC and delta-g-THC) were studied by stimulating primary somatosensory cortex in the cerveau isole squirrel monkey and recording the responses in frontal lobe polysensory areas ipsi- and contralateral to the stimulus, and in the contra-lateral parietal lobe primary somatosensory area, homotopic to the stimulus. Low doses of both THC's increased the amplitudes of the responses and higher doses generally decreased them. Low doses of pentobarbital also produced increases in amplitude and higher doses decreased or abolished the responses. The THC's only slightly decreased the facilitation seen in control recovery cycles, but even low doses of pentobarbital markedly reduced or abolished it. Pentobarbital had its usual effects on the electrocorticogram, i.e., a dose-dependent'flatte'ning with spindling at intermediate doses, but the THC's caused spiking and, at high doses, occasionally a spike and wave pattern. It is suggested that the increased responsiveness of cortical areas produced by the THC's without the concomitant decrease of recovery produced by pentobarbital may be related to the changes in sensory perception produced by the THC's.

BRAESTRUP, C. Effect of phenoxybenzamine, aceperone arid clonidine on the level of 3-methoxy-4-hydroxyphenylglycol (MOPEG) in rat brain. Journal of Pharmacy and Pharmacology 26: 139-141 (1974)

BRAESTRUP, C. Effects of clonidine (catapressan) on synthesis and mettibolism of noradrenaline in the central nervous system of rats. Acta Pharmacologica et Toxicologica 35 (Supplement I): 22 (1974)

For abstract, see Section II: Drug Chemistry and Metabolism.

BRAESTRUP, C. Effects of phenoxybenzamine, aceporone and clonidine on the level of 3-methoxy-4-hydroxyphenylglycol (MOPEG) in rat brain. Journal of Pharmacy and Pharmacology 26 (2): 139-141 (February, 1974)

BRAESTRUP, C. Gas chromatographic evidence for the presence of 3-methoxy-4-hydroxyphenyl-ethanol in rat brain. Biochemical Pharmacology 21: 1775-1776 (1972)

BRAESTRUP, C., NIELSEN, M. and SCHEEL-KRÜGER, J. Feed back mechanisms in central noradrenergic neurones in vivo, investigated through changes in noradrenaline metabolism. Journal de Pharmacologie 5 (Supplement II): 11 (1974)

For abstract, see Section II. Drug Chemistry and Metabolism.

BR ASE, D.A., TSENG. L., LOH, H.H. and WAY, E.L. Cholinergic modification of naloxone-induced jumping in morphine dependent mice. European Journal of Pharmacology 26: 1-8 (1974)

The effects of several i.p. administered, centrally active cholinergic agonists and antagonists on the naloxone-induced jumping behavior of morphine tolerant and dependent mice were studied in an effort to differentiate muscarinic and nicotinic modification of the withdrawal jumping behavior. Nicotine, tremorine, oxotremorine, arecoline and physostigmine significantly inhibited jumping, whereas atropine, benzotropine, pempidine and mecamylamine significantly potentiated jumping. Quaternary cholinergic drugs did not modify jumping. These drug effects were obtained generally without an alteration of the amount of naloxone or morphine in the brain. Cholinergic drugs also modified the jumping incidence in mice undergoing abrupt morphine abstinence. It is concluded that the inhibition of withdrawal jumping in morphine dependent mice by both muscarinic and nicotinic agonists and its enhancement by muscarinic and nicotinic antagonists reflect cholinergic modifications of the jumping response by a central mechanism(s).

BRAUDE, M.C., MANSAERT, R. and TRUITT, E.G., JR. Some pharmacologic correlates to marihuana use. Seminars in Drug Treatment 1(3): 229-246 (December, 1971)

BREESE, G.R., COOPER, B.R. and MUELLER, R.A. Evidence for involvement of 5-hydroxytryptamine in the actions of amphetamine. British Journal of Pharmacology 52: 307-314 (1974)

Pargyline treatment, 1 h before (+)-amphetamine (1 mg/kg), reduced amphetamine-stimulated motor activity. This inhibition was reversed in animals pretreated with p-chlorophenylalanine (PCPA).

Following treatment with PCPA or 5,6-dihydroxytryptamine (5,6-DHT), amphetamine-induced locomotor activity was significantly potentiated. The increased response to amphetamine in PCPA-treated rats was reversed in animals pretreated with 5-hydroxytryptophan.

The inhibition of amphetamine-stimulated locomotor activity by treatment with 6-hydroxydopamine was not reversed by PCPA treatment.

Stereotypies produced by amphetamine were not found to be altered by depletion of 5-hydroxytryptamine.

Induction of adrenal tyrosine hydroxylase activity produced by chronic amphetamine administration was significantly potentiated by PCPA, emphasizing the involvement of a 5-hydroxytryptamine inhibitory system in more than one action of amphetamine.

BREESE. G.R., COOPER, B.R. and SMITH. R.D. Biochemical and behavioural alterations following 6-hydroxydopamine administration into brain. Frontiers in Catacholamine Research. Edited by E. Usdin and S. H. Snyder. New York: Pergamon Press, 1973.

Adult and neonatal rats treated with 6-OHDA to reduce NE, DA or both catecholamines have been used to examine the role of brain catecholamines in several behaviours. The data implicated DA-containing fibres in the maintenance of several diverse functions including consummatory behaviour, active avoidance responding and self-stimulation of brain. Motor activity and stereotypies induced by amphetamine also appear to be dependent upon brain DA. Table 1 shows that brain NE at this time has been associated only with temperature control. Present findings are consistent with proposals (Everett and Wiegand, 1962; Seiden and Carlsson, 1963) suggesting alternative roles for DA not clearly related to its usual association with extrapyramidal function.

BRIDGE, T.P. and ELLINWOOD, E.H., JR. Quaalude alley: A one-way street. American Journal of Psychiatry 130(2): 217 (1972)

BRISTER. C.C. and DAVIS, W.M. Antagonism of acute lethality of narcotic analgesics in aggregated and isolated mice by the central cholinomimetic action of pilocarpine. Archives internationales de Pharmacodynamie et de Therapie 210(2): 298-305 (August, 1974)

The central cholinomimetic action of pilocarpine hydrochloride, in combination with the peripherally-acting anticholinergic methylatropine bromide (1.0 mg/kg i.p.), was tested for ability to protect mice against acute toxicity of 5 analgesics. Pilocarpine (10-30 mg/kg i.p.) pretreatment reduced lethality after morphine, meperidine, levorphanol, methadone and pentazocine in aggregated mice, but failed to antagonize lethality after d-amphetamine. In isolated mice the effect of pilocarpine was comparable to that for aggregated mice for the latter 3 analgesics. However, a higher dose was required to antagonize mortality of isolated mice after meperidine, which caused the most prominent excitation among the analgesics. Moreover, no protection was found against morphine, but instead a toxic synergism. Symptomatic observations suggested both central depressant and excitatory effects of pilocarpine which seemed to interact with similarly mixed central effects of the analgesics in a complex fashion, varying among the several analgesics. Observations that atropine sulfate (3.0 mg/kg i.p.) completely prevented the protective action of pilocarpine. while methacholine chloride (10 mg/kg i.p.) plus methylatropine (1.0 mg/kg) failed to afford protection, substantiate a central site for the action of pilocarpine.

BROWN, D.J., MILLER, F.N., LONGNECKER, D.E., GREENWALD, E.K., HARRIS. P.D. and FORNEY, R.B. The influence of delta-9-tetrahydrocannabinol on cardiovascular and subcutaneous microcirculatory systems in the bat. The Journal of Pharmacology and Experimental Therapeutics 188(3): 624-629 (1974)

For abstract, see Section II. Drug Chemistry and Metabolism.

BUNNEY, B.S. and AGHAJANIAN, G.K. A comparison of the effects of chlorpromazine, 7-hydroxychlorpromazine and chlorpromazine sulfoxide on the activity of central dopaminergic neurons. Life Sciences 15(2): 309 (July, 1974)

Using single unit recording techniques, chlorpromazine (CPZ) and two of its naturally occurring metabolites in man, 7-hydroxychlorpromazine and CPZ sulfoxide. were tested for their ability to reverse amphetamine induced depression of rat dopaminergic ventral tegmental neurons. Small equivalent doses of CPZ and 7-hydroxychlorpromazine were found to readily reverse amphetamine induced depression of these cells. CPZ sulfoxide was found to be 50-100 times less potent in this regard. On the basis of this and other evidence, it is suggested that 7-hydroxychlorpromazine may be a good antipsychotic agent.

BUNNEY, B.S. and AGHAJANIAN, G.K. Electrophysiological effects of amphetamine on dopaminergic neurons. Frontiers in Catecholamine Research. Edited by E. Usdin and S. Snyder. New York: Pergamon Press, 1973.

D-amphetamine (D-AMP) administered intravenously in low doses markedly depresses the firing rate of dopaminergic neurons. This effect of D-AMP appears dependent upon the presence of ongoing synthesis as it is abolished by alpha-methyl-P-tyrosine (AMPT) (a tyrosine hydroxylase inhibitor) and by high doses of R04-4602 (a decarboxylase inhibitor). The previously proposed hypothesis that D-AMP depresses DA cell firing rate indirectly via a postsynaptic nondopaminergic feedback pathway was confirmed. This conclusion is based on the following findings: 1) as predicted, D-AMP selectively depresses the firing rate of dopaminergic neurons in the substantia nigra zona compacta and adjacent ventral tegmental; 2) the direct effect of D-AMP on DA cell activity when applied iontophoretically, even with high ejection currents, is weak and transient as compared to its marked depressant effect when applied with low currents in the vicinity of postsynaptic neurons (i. e. neurons receiving a dopaminergic input): and 3) transaction between the substantia nigra and striatum abolishes the depressant effect on DA cell firing rate of systemically administered D-AMP. The latter result strongly suggests the existence of a neuronal feedback pathway although its precise anatomical location has yet to be determined.

BUNNEY, B.S. and AGHAJANIAN, G.K. Electrophysiological effects of amphetamine on dopaminergic neurons. Life Sciences 13(4): 14 (1973)

The electrophysiological effects of amphetamine on dopaminergic neurons was examined in the rat. To evaluate the proposed suggestion that amphetamine, by increasing the concentration of dopamine (DA) postsynaptically, may initiate a neuronal feedback inhibition of DA cells, its effect on the firing rate of dopaminergic neurons was determined by single unit recordings. Recordings were made from the DA containing cells in the zona compacta of the substantia nigra and adjacent ventral tegmental area of the rat midbrain. D-amphetamine was potent in decreasing the spontaneous activity of DA neurons. Pretreatment with alpha-methyl-paratyrosine blocked this depressant effect and reversed it when given after amphetamine. Haloperidol and cholorpromazine both prevented and reversed the amphetamine induced depression of the firing rate. It is assumed that ongoing synthesis of DA is necessary for D-amphetamine to exert its effect and that DA receptors may be involved in amphetamine's ability to depress DA neurons. Tests were made to rule out the possibility that amphetamine might have a direct effect on dopaminergic cells. The hypothesis that amphetamine releases newly synthesized DA which in turn affects DA cell firing via a postsynaptic feedback pathway was supported.

BURKS, T. Mediation by 5-hydroxytryptamine of morphine stimulant actions in dog intestine. The Journal of Pharmacology and Experimental Therapeutics 185(3): 530 (1973)

Intestinal contractor effects of morphine, 5-hydroxytryptamine (5-HT) and cholinergic agonists were investigated in sections of dog small intestine perfused in vitro with Krebs' solution. Morphine and 5-HT produced similar patterns of intestinal hypermotility characterized by initial tonic increases in intraluminal pressure and pronounced secondary phasic contractions. The morphine-induced hypermotility could not have resulted from extrinsic influences on the isolated segments of bowel. Cholinergic agonists generally. produced only brief tonic contractions of the intestinal smooth muscle. Treat-, ment of dogs with reserpine to deplete local stores of 5-HT selectively reduced intestinal responses to morphine. This indicated that release of endogenous 5-HT initiates the spasmogenic response to the narcotic. The contractor effects of 5-HT and morphine were diminished by tetrodotoxin, nicotine depolarization and atropine but not by tetraethylammonium. These data demonstrate that a significant portion of the stimulatory action of the 5-HT released by morphine results from activation of intramural cholinergic nerve elements which differ from those activated by conventional ganglionic stimulants. Experiments with the 5-HT receptor blocking drugs, cinanserin and cyproheptadine, indicate that the 5-HT mobilized by morphine also exerts direct stimulatory actions on smooth muscle 5-HT receptors. The hypermotility of the dog bowel induced by morphine thus appears to result from release of local intestinal 5-HT. The 5-HT liberated by morphine exerts both direct and indirect exitatory smooth muscle effects. The indirect component of 5-HT action is mediated by cholinergic nerve elements in the wall of the intestine:

BURKS. T.F. and GRUBB. M.N. Sites, of acute morphine tolerance in intestine. The Journal of Pharmacology and Experimental Therapeutics 191: 518 (1974)

Experiments were performed to differentiate between neurotransmitter receptors and narcotic receptors as sites for acute narcotic tolerance in dog intestine. Intestinal motor responses to bolus intra-arterial injections of morphine, 5-hydroxytryptamine (5-HT), bethanechol and dimethylphenylpiperazinium were measured in isolated small bowel segments. The vasculature of the isolated segments was perfused with Krebs-bicarbonate 'solution (control) or with Krebs' solution containing morphine, levorphanol, naloxone or 5-HT. During perfusion of gut segments with morphine (2 mu-g/ml), intestinal motor responses to bolus doses of morphine were significantly reduced (acute tolerance). Responses to 5-HT, bethanechol and dimethylphenylpiperazinium were not reduced., Perfusion of segments with levorphanol (0.2 mu-g/ml) reduced responses to 5-HT slightly and reduced responses to morphine considerably. Levorphanbl did not alter responses to bethanechol and dimethylphenylpiperazinium. Naloxone (2 mu-g/ml) 'perfusion, like morphine perfusion, reduced responses to morphine selectively, Responses to both morphine and 5-HT were reduced during perfusion of bowel segments with 5-HT (20 mu-g/ml). Previous studies have indicated that both 5-HT and cholinergic receptors are involved in the intestinal stimulatory response to morphine (Burke, T. F. J. Pharmacol. Exp. Ther. 185: 530-539, 1973). Acute tolerance of tachyphylaxis to the narcotics, however, did not prevent responses to 5-HT, and the cholinergic agonists., These observations thus suggest that acute tolerance to morphine results from events expressed at the level of the narcotic receptor. Reduced responsiveness to morphine occurs during, tachyphylaxis to 5-HT apparently because morphine's stimulatory effects are mediated in part by 5-HT.

BURKS, T.F., JAQUETTE. D.L. and GRUBB, M.N. Development of tolerance to the stimulatory effect of morphine in dog intestine. European Journal of Pharmacology 25: 302-307 (1974)

Intestinal motor responses to morphine and 5-hydroxytryptamine (5-HT) were measured in dogs injected daily for 16 days with morphine (stabilized at 30 mg/kg i.v.) and compared to responses obtained in control animals. Intestinal contractions produced by 10 and 20 mu-g/kg morphine were reduced in the morphine-treated animals. Responses to 5-HT did not differ between the two groups. The contractor dose-response curve for morphine, but not for 5-HT or bethanechol, was shifted markedly to the right in intestinal segments isolated from morphine-treated dogs. It is concluded that tolerance to the intestinal stimulatory effect of morphine occurs in the dog.

BURSTEIN, S., LEWIS, E. and VARANELLI. C. Prostaglandins and cannabis - II: Inhibition of biosynthesis by the naturally occurring cannabinoids. Biochemical Pharmacology 22: 2905-2910 (1973)

A series of the naturally occurring cannabinoids were tested for possible effects on the biosynthesis of prostaglandins. Most of the substances examined were able to inhibit in varying degrees the conversion of 8,11,14-eicosatrienoic acid to prostaglandin E_1 (PGE_1) when incubated with bovine seminal vesicle microsomes. The order of activity starting with the most potent was cannabinol, cannabidioIic acid, delta-6-tetrahydrocannabinol (delta-6-THC), cannabidiol, bichromene and delta-1-THC; cannabicyclol showed almost no inhibitory activity. It is suggested that certain of the pharmacological actions of some of these cannabinoids may be explained by a similar effect in vivo. Olivetol, which represents a partial structure for all of the compounds tested, showed high activity, indicating that the inhibitory power of the cannabinoids resides in the aromatic portion of the molecule.

BURSTEIN, S. and MECHOULAM. R. Stereospecifically labelled delta-1(6)-tetrahydrocannabinol. Journal of the American Chemical Society 90: 2420 (1968)

BURSTEIN, S.H., MENEZES, F., WILLIAMSON, E. and MECHOULAM, R. Metabolism of delta-1(6)-tetrahydrocannabinol, an active marihuana constituent. Nature 225: 87-88 (1970)

BURSTEIN, S. and RAZ, A. Inhibition of prostaglandin E_2 biosynthesis by delta-1-tetrahydrocannabinol. Prostaglandins 2(5): 369 (1972)

BUXBAUM, D.M. Analgesic activity of delta-9-tetrahydrocannabinol in the rat and mouse. Psychopharmacologia 25: 275-280 (1972)

An analysis of the analgesic activity of delta-9-tetrahydrocannabinol (delta-9-THC) was carried out in rats and mice using both the hot plate and tail flick tests. In the rat, the dose-effect curve of delta-9-THC was comparable to that of morphine in both tests. In the mouse, however, the THC dose-effect curves were more variable and less steep than the morphine dose-effect curves. THC was less potent than morphine in both tests in mice. THC analgesia reached its peak at one hour and had a longer duration of action than morphine.

BUXBAUM, D.M., BUSHING, J.A., CARTER, M.E. and SANDERS-BUSH, E. Long-term effects of p-chloroamphetamine (PCA) on cerebral serotonic (5HT) and morphine (M)-induced locomotor activity in the rat. Presented at the Fifth International Congress on Pharmacology, San Francisco, California, 1972.

BUXBAUM, D. and SCHMIDT, D.E. Modification of motor induced motor effects by cholinergic antagonists and effects of morphine on regional ACH utilization in rat. Federation Proceedings, (in press)

CARINO, M.A. and HORITA, A. The monoamine oxidase activity of the hamster gastro-intestinal tract. Proceedings of the Western Pharmacological Society 12: 25 (1969)

CAVERO, I., BUCKLEY, J.P. and JANDHYALA, B.S. Hemodynamic and myocardial effects of (-)-delta-9-trans-tetrahydrocannabinol in anesthetized dogs. European Journal of Pharmacology 24: 243-251 (1973)

(-)-Delta-9-trans-tetrahydrocannabinol (delta-9-THC) (39 mu-g-2.5 mg/kg, i.v.) decreased blood pressure, heart rate, cardiac output and right ventricular contractile force in a dose-related manner in intact dogs under pentobarbital anesthesia. The delta-9-THC-induced hypotension appeared to result mainly from a consistent and reproducible attenuation of cardiac output since no marked alteration in total peripheral resistance occurred. In these animals the decrease in cardiac output appeared to be related to the bradycardia since there was no change in stroke volume following delta-9-THC. However, when the change in heart rate was prevented by atria1 pacing or cardiac denervation, a less but significant reduction in cardiac output was induced by delta-9-THC. Under these experimental conditions delta-9-THC also significantly attenuated stroke volume. In contrast, delta-9-THC did not induce any significant changes in cardiac output, blood pressure, and heart rate of dogs pretreated with a ganglionic blocker.

Delta-9-THC appeared to be devoid of any measurable direct effect on the myocardium since the compound neither significantly altered right ventricular contractile force of the denervated or ganglionic blocker-pretreated hearts nor interfered with the positive inotropic responses to i.v. calcium and isoproterenol.

In the major vessel occlusion preparation administration of delta-9-THC was followed by a reduction in venous tone. Furthermore, measurements of blood and plasma volume excluded an effect of delta-9-THC in these parameters.

From these findings it is suggested that the reduction in cardiac output induced by delta-9-THC is the result of the action of this compound on cardiac rate as well as venous return; no evidence could be documented for a direct effect of this compound on the myocardlum.

CAVERO, I., BUCKLEY, J.P. and JANDHYALA, G.S. Parasympatholytic activity of (-)-delta-9-trans-tetrahydrocannabinol in mongrel dogs. European Journal of Pharmacology 19(2): 301-304 (1972)

The compound (-)-delta-9-trans-tetrahydrocannabinol (delta-9-THC) (0,312-5 mg/kg) shifted the frequency - response curves of vagal stimulation to the right and attenuated salivation induced, by chorda tympani stimulation in dogs. This parasympatholytic activity of delta-9-THC was neither atropine like nor due to ganglionic blockage. It is postulated. that delta-9-THC may interfere, with the release of acetylcholine.

CAVERO, I., ERTEL, R., BUCKLEY, J.P. and JANDHYALA, B.S. Effects of (-)-delta-9-trans-tetrahydrocannabinol on regional blood flow in anesthetized dogs, European Journal of Pharmacology 20: 373-376 (1972)

Distribution of cardiac output to various organs was studied utilizing Sr-labelled microspheres in dogs. In the group receiving delta-9-THC, 2.5 mg/kg, i.v., there was a significant reduction in the fractional blood flow accompanied by an increase in resistance in the splanchnic vasculature. Net total peripheral resistance was unchanged.

CAVERO, I., KUBENA, R.K., DZIAK, J., BUCKLEY, J.P. and JANDHYALA, B.S. Certain observations on interrelationships between respiratory and cardiovascular effects of (-)-delta-9-trans-tetrahydrocannabinol. Research Communications in Chemical Pathology and Pharmacology 3(3): 483-492 (May, 1972)

The effects of (-)-delta-9-trans-tetrahydrocannabinol (delta-9-THC), a pharmacologically active constituent of marihuana, on the cardiovascular and respiratory system was investigated in mongrel dogs under pentobarbital anesthesia. Delta-9-THC (5 mg/kg, i.v.) caused a transient hypernea and hypoxic hypoxia in spontaneously breathing animals; however, no alterations in the blood gas parameters were observed in artificially ventilated animals. The delta-9-THC induced hypotension reached its maximum within 15 minutes in animals maintained at a constant arterial pO_2, but this effect was significantly attenuated during the hypoxemic state in the spontaneously breathing animals. The present data suggest that the full hypotensive activity of delta-9-THC may be prevented by hypoxic hypoxia, however, the bradycardic effect of this compound was profound and independent of any alterations on blood gas parameters.

CAVERO, I., LOKHANDWALA, M.F., BUCKLEY, J.P. and JANDHYALA, B.S. The effect of (-)-delta-9-trans-tetrahydrocannabinol on myocardial contractility and venous return in anesthetized dogs. European Journal of Pharmacology 23: 74-82 (1974)

Administration of (-)-delta-9-trans-tetrahydrocannabinol (delta-9-THC, 2.5 mg/kg i.v.) to pentobarbital-anesthetized dogs in which heart rate was maintained constant by electrical pacing, decreased aortic blood pressure, cardiac output, left ventricular, peak pressure and left ventricular end diastolic pressure and dP/dt. However, the contractility index (max. dp/dt)/I.P. was not altered by the compound, Furthermore, it was shown that the decrease in cardiac output due to delta-9-THC could be restored to original levels by an infusion of saline-dextran in quantities sufficient to elevate the left ventricular end diastolic pressure to pre-delta-9-THC level.

In dogs in which cardiac output was maintained constant by a right heart bypass procedure delta-9-THC decreased blood pressure and total peripheral resistance and augmented intravascular blood volume. This increase in intravascular blood volume was significantly less (74%) in animals in which the splanchnic (superior, inferior, and celiac) arteries were ligated prior to the administration of delta-9-THC. On the other hand, in spinal dogs delta-9-THC was devoid of any measurable cardiovascular effects.

These observations clearly support the hypothesis that the diminution of cardiac output induced by delta-9-THC in animals with constant cardiac rate is primarily due to dominished venous return to the heart and not to an impaired ability of the myocardium.

CAVERO, I., SOLOMON, T., BUCKLEY, J. P. and JANDHYALA, G.S. Studies on the bradycardia induced by (-)-delta-9-trans-tetrahydrocannabinol in anesthetized dogs. European Journal of Pharmacology 22(3): 263 (1973)

Decreased heart rate resulted from (-)-delta-9-trans-tetrahydrocannabinol (delta-9-THC) in a dose related manner in dogs under pentobarbital anesthesia. This cardiac effect of delta-9-THC was neither due to an impairment of transmission across the sympathetic ganglia nor to a specific stimulation of parasympathetic ganglia. Selective blockade of either parasympathetic (atropine, bilateral vagotomy) or sympathetic (propranolol, spinal section at C2-C4) neurogenic activity to the heart partially 'prevented the negative chronotropic effect of THC. However, the bradycardic effect of delta-9-THC was completely abolished in animals in which the autonomic pathways to the heart were pharmacologically or surgically inactivated. Administration of delta- 9-THC into the vascularly isolated, neurally intact cross-perfused head of dogs significantly slowed the. heart rate in intact as well as debuffered recipients. This bradycardia was reduced in recipients in which the trunk was atropinized prior to cerebral administration of delta-9-THC. Injection of delta-9-THC into the femorai vein of the recipient in the dog cross circulation preparation also caused a significant decrease in heart rate which was essentially abolished either by bilateral vagotomy or by atropinization of the recipients. These results are compatible with the hypothesis that the negative chronotropic effects of delta-9-THC in dogs under pentobarbital anesthesia is of central origin and involves both a direct and reflexogenic alteration of central autonomic outflow regulating the heart rate.

CHAPEL, J.L. and TAYLOR, D.W. Drugs for kicks. Crime and Delinquency 16(1): 1-35. (1970)

This paper is a review of drugs that are being used by children and adolescents. In discussing the sniffing of glue, gasoline, thinners, and lighter fluid, the use of narcotics, hallucinogenic drugs, and rare and exotic hallucinogens, topics such as general information, effects, techniques of administration, habit description, clinical findings, association with crime, and others are discussed. Inhaling noxious vapors may result in acute brain syndrome resembling alcohol intoxication plus hallucinations and delusions. The resulting deterioration of judgment sometimes leads to serious accidents and possible fatal consequences. More serious is the problem of the adolescent narcotic addict who is under severe compulsion to obtain drugs, often illegally, to feed his physical and psychic craving. Lysergic acid diethylamide (LSD) and marihuana are the most commonly abused hallucinogens. Although neither has been shown to be addictive, both produce physiologic and psychic manifestations that can be severe, and both can precipitate psychotic breaks. LSD has been shown to cause chromosomal breaks in the cells of users and their offsprings. Other drugs such as morning glory seeds, nutmeg, and peyote are used less frequently but give the same reactions. The paper conjectures that the use of LSD, 2, 5-dimethoxy-4-methylamphetamine (STP), and other psychedelic drugs, but not marihuana, will eventually decrease but that other modes of getting kicks will spring up to take their place.

CHAU, T.T., DEWEY, W.L. and HARRIS, L.S. Mechanism of the synergistic lethality between pentazocine and vasopressin in the rat. The Journal of Pharmacology and Experimental Therapeutics 186(2): 288 (1973)

Findings in a study of the mechanism of the synergistic lethality between pentozocine and vasopressin show that pentazocine injected immediately before vasopressin caused a significantly greater mortality in rats than when either compound was given alone. This effect was not observed in either mice or dogs. There was no alteration of the lethality of pentazocine in mice when injections of vasopressin were given immediately after the narcotic - antagonist analgesic. Vasopressin reduced the magnitude and duration of the behavioral effects of pentazocine in dogs. Oxytocin did not potentiate the lethality of prntazocine in rats. Pentazocine and vasopressin caused cardiac and respiratory depression leading to death in anesthetized rats but not in anesthetized dogs. The synergistic lethality of these compounds in rats was not blocked by prior injections of tripelennamine or atropine. Vagotomy did not block the synergistic lethality in the anesthetized rats. Vasopressin significantly increased the level of pentazocine in rat brain and heart, but not in mice. Oxytocin which did not increase the lethality of pentazocine, also did not alter the level of pentazocine in rat brain tissue.

CHENEY, D.L. and GOLDSTEIN, A. The effect of rho-chlorophenylalanine on opiate-induced running, analgesia, tolerance and physical dependence in mice. The Journal of Pharmacology and Experimental Therapeutics 177(1): 309-315 (1971)

For abstract. see Section II. Drug Chemistry and Metabolism.

CHENEY, D.L. and GOLDSTEIN, A. Tolerance to opioid narcotics, III. Time course and reversibility of physical dependence in mice. Nature 232: 477 (1971)

CHENEY, D.L., GOLDSTEIN, A., ALGERI, S. and COSTA, E. Narcotic tolerance and dependence: Lack of relationship with brain serotonin turnover. Science 171: 1169 (1971)

For abstract, see Section II. Drug Chemistry and Metabolism.

CHENEY, D.L., GOLDSTEIN, A. and SHEEHAN, P. Rate of development and reversibility of brain tolerance and physical dependence in mice treated with opiates. Federation 29(2): 685 (March-April, 1970)

For abstract. see Section II. Drug Chemistry and Metabolism.

CHENEY, D.L., JUDSON, B. A. and GOLDSTEIN, A. Failure of an opiate to protect mice against naloxone-precipitated withdrawal. The Journal of Pharmacology and Experimental Therapeutics 182(2): 189-194 (1972)

Mice were made dependent upon the opiate narcotic. levorphanol, by repeated injections of a fixed dose at a four- or eight-hour interval. The degree of dependence was measured by determining the ED50 of naloxone for eliciting jumping activity. After dependence was established. on either schedule, the greatly increased plasma and brain levels of the agonist (levorphanol) after an injection did not cause any increase in the ED50 of the antagonist (naloxone). The behavior of antagonists in blocking primary opiate effects is competitive. In contrast, the results reported here indicate that even a large increase of levorphanol concentration in brain does not protect against naloxone precipitated withdrawal.

CHIPKIN, R.E., DEWEY, W.L. and HARRIS, L.S. The effect of propanolol on the antinociceptive and opiate withdrawal characteristics of morphine in mice. The Pharmacologist (in press)

Reports have implicated the beta-adrenergic system in the actions of morphine (M) and suggested blocking this system might be usefulin alleviating opiate withdrawal in man. In this study, male albino mice weighing between 16 and 30 g were used. All injections were given i.p. Propranolol (P), at a dose (10 mg/kg) which did not alter tail flick latency by itself, did not alter the ED50 of M when given 10 minutes prior to the narcotic (ED50 for M = 9.2 mg/kg and for P + M = 9.8 mg/kg). The s.c. implantation of a 75 mg M pellet caused physical dependence in mice as evidenced by the naloxone (N) induced jumping test. Propranolol at doses of 10 and 25 mg/kg given 10 mins. prior to N challenge did not significantly alter'either the frequency of N induced, jumping or the ED50 of N in the chronic morphinized mice (ED50 for N = 0.029 mg/kg and for P + N = 0.035 mg/kg). N caused hypoactivity in mice when administered 72 hours after M pellet implantation. An injection of 10 or 25 mg/kg P 10 mins. prior to N caused greater hypoactivity rather than reversing the effects of N. These data suggest that the beta-adrenergic blocking agent, P, does not alter the antinociceptive activity or lessen the withdrawal syndrome of M in mice.

CHOULIS. N.H. and PAPADOPOULOS. H. Long acting methadone. Journal of Pharmaceutical Science (in press)

CHRISTENSEN, C., BEST, J.F. and HERIN, R.A. Changes seen in the electroencephalogram and heart rate in the rat after administration of marihuana intravenously. Federation Proceedings 30(2): 375 (1971)

The intravenous administration of marihuana red oil affected septal activity in the rat and altered septal - hippocampal activity. Both the dorsal septum and hippocampal frequencies decreased and the power spectrums increased, but these changes were more pronounced in the dorsal septum.

CICERO, T.J. and MEYER, E.R. Morphine pellet implantation in rats: Quantitative assessment of tolerance and dependence. The Journal of Pharmacology and Experimental Therapeutics 184(2): 404-408 (1973)

For abstract, see Section I. Methodology of Drug Research.

CICERO, T.J., MEYER, E.R., BELL, R.D. and WIEST, W.G. Effects of morphine on the secondary sex organs and plasma testosterone levels of rats. Research Communications in Chemical Pathology and Pharmaco1ogy 7(1): 17-24 (January, 1974)

A 3 day period of morphine pellet implantation produced a marked reduction in the wet and dry weights of the seminal vesicles and prostate glands of the rat. In the seminal vesicles, there was also a marked decrease in secretory activity. The apparent atrophic changes in these important accessory sex organs appears to be related to a pronounced morphine induced lowering of plasma testosterone levels.

CICERO, T.J., MEYER. E.R. and SMITHLOFF, B.R. Alpha adrenergic blocking agents: Antinociceptive activity and enhancement of morphine-induced analgesia. The Journal of Pharmacology and Experimental Therapeutics 189(1): 72-82 (April, 1974)

For abstract, see Section II. Drug Chemistry and Metabolism.

CICERO, T.J., SHARPE, L.G., WILCOX, C.E. and SMITHLOFF, B.R. Effects of morphine in vivo and in vitro on tyrosine hydroxylase activity in rat brain. The Journal of Pharmacology and Experimental Therapeutics (in press)

CICERO, T.J., WILCOX, C.E., SMITHLOFF, B.R.. MEYER, E.R. and SHARPE, L.G. Effects of morphine, in vitro and in vivo, on tyrosine hydroxylase activity in rat brain., Biochemical Pharmacology 22(24): 3237-3246 (December, 1973)

For abstract, see Section II. Drug Chemistry and Metabolism.

CLINESCHMIDT, V. and HORITA, A. Auto-potentiation by inhibition of monoamine oxidase of the sympathomimetic action of phenelzine and pheniprazine. British Journal of Pharmacology and Chemotherapy 30: 67-77 (1967)

CLONINGER, C.R., PACKMAN, P.M., CICERO, T.J., BOSHANS, R.L. and ROBINS, E. Morphine dependence and enzyme activity in the hypothalamus. Biochemical Pharmacology 23(5): 983-988 (March. 1974)

For abstract, see Section II. Drug Chemistry and Metabolism.

CLOUET, D.H. The alteration of brain metabolism by narcotic analgesic drugs. Handbook of Neurochemistry, Vol. 6. Edited by A. Lajtha, New York: Plenum Press, 1970. Pp. 479-508.

The administration of narcotic analgesic drugs to experimental animals has a profound effect on metabolism in the central nervous system. Alterations have been observed in protein, nucleic acid, lipid, and energy metabolism. In addition, the biogenic amines and the pituitary -adrenal hormonal mechanisms are implicated in the biochemical response to narcotic drugs. Because all of the metabolic systems in brain are in a delicate equilibrium, responsive to the slightest change in chemical environment, it is likely that most of the observed effects are secondary shifts consequent to the initial biochemical lesion. Such factors as the competition between acetylcholine and morphine for hydrolysis and transport, the release in vivo of serotonin and norepinephrine by morphine, the inhibition of proteinmbonucleic acid synthesis by narcotic drugs, the effects of the drugs on membrane phospholipids and on the loss of ATP in single cells, all suggest possible sites of action for the drugs. The possibility that there is more than one biochemical site of action should be considered, both because of the many responses to drug administration in biochemical and pharmacological parameters, and because of the structural similarities between narcotic analgesic drugs and tissue components such as steroid hormones and the biogenic amines.

Whatever the site of the biochemical lesion in the central nervous system produced by a single injection of a narcotic drug, it is apparent that there are two general responses to chronic drug administration: (1) less response, or the 'absence of any response during chronic drug treatment in a system which shows change after a single dose, or (2) an increased-response to chronic treatment. In the first category of responses are the effects on K^+-stimulated oxygen and glucose uptake by brain slices, the release of Ca^{2+} in the brain in vivo, the release of hypothalamic pituitary-hormone-releasing factors, trophic hormones from the pituitary and the changes in biogenic amines in the central nervous system. These may be considered adaptive responses related to pharmacological tolerance since the effect of the initial injection is reversed by chronic drug use. In the second category of response are the effects on the synthesis of brain proteins and of biogenic amines, which show larger changes with chronic drug administration. An attractive hypothesis, for which the evidence is not conclusive, is that these metabolic systems are part of the control mechanism for attaining new equilibria in the biochemical systems of the first category, i.e., the mechanism for the development of tolerance.

An important question remains unanswered: whether the sum total of the biochemical responses in the central nervous system to the administration of narcotic drugs represent a major disturbance of brain metabolism, or instead, a minor transient effect qualitatively, and quantitatively, similar to events occurring often in the CNS as a result of other modes of stimulation.

CLOUET, D.H. Cellular biochemistry of narcotic analgesic drugs in the central nervous system of the rat. Psychiatric Quarterly 46(3): 384-392 (1972)

For abstract, see Section II. Drug Chemistry and Metabolism.

CLOUET, D.H. The effects of drugs on protein synthesis in the nervous system. Protein Metabolism of the Nervous System. Edited by A. Lajtha. New York: Plenum Press, 1970. Pp. 699-713.

For abstract, see Section II. Drug Chemistry and Metabolism.

CLOUET, D.H. Effects of narcotic analgesics on brain function. Biolopy of Brain Dysfunction, Vol. II. Edited by G. Guall. New York: Plenum Press, 1973. Pp; 115-149.

The ubiquitous role played by narcotic analgesics in altering metabolism in single cells; in inhibiting simple polysynaptic reflexes in the spinal dog, in affecting the regulation of body temperature in the decorticate dog, and in modulating behavior in intact animals and man may be attributed to a wide distribution of receptor sites for drug activity in both the central and peripheral nervous systems. Because the narcotic drugs are large ionizable organic molecules, they enter the nervous system readily and are distributed throughout the brain and in peripheral nerve. The localization of the drugs in gross anatomical or subcellular areas of the CNS seems to be more dependent on physicochemical characteristics of each drug than on the relative pharmacological action of the drug. In homologous series of drugs, correlations have been made between narcotic activity and one or more physicochemical characteristics, such as partition coefficients or dimensions of lipophilic sites. Comparisons of the "analgesic receptor(s)" as defined by structural modifications in various families of narcotics suggest that the "receptor" may exist in more than one conformation with varying numbers of binding sites. This suggestion would offer a chemical basis for the varying pharmacological effects produced by administration of the various types of narcotic analgesics.

On the subcellular level, the localization of radiolabeled narcotic drugs after administration in active doses to animals in the nerve-ending fractions isolated from the CNS, and especially in the membranes obtained from reptured nerve-endings. may offer a clue to the localization of the "receptor." If the synaptic membrane is the site of drug action, and synaptic transmission is the function which is disturbed, then secondary effects arising from these primary lesions could involve the biogenic amines and acetylcholine in the CNS and elsewhere and the hypothalamic-pituitary-adrenal system, which in turn would produce alterations in the neurohormonal modulation of the CNS. This progression would lead to's new equilibrium in neuronal functioning established to counter the drug effects. It is possible to include most physiological and biochemical responses to drug administration in this scheme of events. The development of tolerance to and dependence on chronic drug use could then be considered as adaptive responses to the effects of the drug through mechanisms as yet unknown.

CLOUET, D.H. Role of catecholamines in action of narcotic drugs. Catecholamines and Behavior. Edited by A. Friedhoff. New York: Plenum Press, 1974.

CLOUET, D.H. Theoretical biochemical mechanisms for drug dependence. Chemical and Biological Aspects of Drug Dependence. Edited by S.J. Mule and H. Brill. Cleveland, Ohio: Chemical Rubber Company Press, 1972. Pp. 545-551.

CLOUET, D.H., JOHNSON, J.C., RATNER, M., WILLIAMS, N. and GOLD. G. J. The effect of morphine on rat brain catecholamines: Turnover in vivo and uptake in isolated synaptosomes. Frontiers in Catecholamine Research. Edited by E. Usdin and S. H. Snyder. New York: Pergamon Press, 1973.

CLOUET, D.H. and NEIDLE. A. The effect of morphine on the transport and metabolism of intracisternally-injected leucine in the rat. Journal of Neurochemistry 17: 1069-1074 (July, 1970)

For abstract, see Section II. Drug Chemistry and Metabolism.

CLOUET, D.H. and RATNER, M. The biosynthesis of catecholamines in the brains of morphine treated rats. Committee on Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council, 1970. P. 7025.

CLOUET, D.H. and RATNER, M. Catecholamine biosynthesis in the brains of morphine-treated rats. Science 168: 854-856 (May, 1970)

For abstract, see Section II. Drug Chemistry and Metabolism.

CLOUET, D.H. and RATNER, M. Effect of morphine on brain tyrosine hydroxylase activity. Federation Proceedings 30: 501 (1971)

For abstract, see Section II. Drug Chemistry and Metabolism.

CLOUET, D.H. and WILLIAMS, N. The effect of narcotic analgesic drugs on the uptake and release of neurotransmitters in isolated syniptosomes. The Journal of Pharmacology and Experimental Therapeutics 188(2): 419-428 (February, 1974)

For abstract, see Section II. Drug Chemistry and Metabolism.

COCHIN, J. Factors influencing tolerance to and, dependence on narcotic analgesics. Opiate Addiction: Origins and Treatment. Edited by S. Fisher and A. Freedman. Washington, D. C.: V. H. Winston and Sons, Inc., 1974.

COCHIN, J. Possible mechanisms in the development of tolerance. Federation Proceedings 29(1): 19-27 (1970)

COCHIN, J. Tolerance to the narcotic analgesics: A long term phenomenon, Proceedings of the Symposia held at the VIII Congress of the Collegium Internationale Neuro-Psychopharmacologicum, Copenhagen, Denmark; August, 1972.

COCHIN, J. and FEINBERG, M.P. Inhibition of development of tolerance to morphine by cycloheximide. Biochemical Pharmacology 21: 3082 (1972)

COCHIN, J. and KORNETSKY, C. Factors in blood of morphine-tolerant animals that attenuate or enhance effects of morphine in nontolerant animals. The Addictive States, Vol. XLVI. Association for Research in Nervous and Mental Disease. Baltimore; Maryland: The Williams and Wilkins Company, 1968.

COHEN, A.H. and BOWERS, M.B., JR. 5-hydroxyindoleacetic acid in rat forebrain and cerebrospinal fluid following dorsal and median midbrain raphe lesions. Brain Research 39: 519-522 (1972)

COHEN, S., DITMAN, K.S. and HAYMAN, M., editors. Symptoms and signs of drug abuse: Continuing. Drug Abuse and Alcoholism Newsletter 1(10): 1-4 (December, 1972)

As part of a continuing report on the organic side effects of drug misuse, cardiovascular, gastrointestinal, hematopoietic. musculoskeletal, neurological, and psychiatric drug induced dysfunctions are described.

COHN, M.L. Acute behavioral changes induced in the rat by the intracerebroventricular administration of thyrotropin releasing factor (TRF) and somatostatin. Proceedings of the Society of Toxicology, Williamsburg, Virginia, March 9-13, 1975.

COHN, M.L. Cyclic AMP, thyrotropin releasing factor (TRF) and somatostatin - key factors in the regulation of the. duration of narcosis. Molecular Mechanisms of Anesthesia. Edited by B.R. Fink. New York: Raven Press, 1975.

COHN, M.L. Dibutyryl cyclic AMP - an antidote to hypnotic, sedative and tranquilizer overdosage in the rat. Toxicology and Applied Pharmacology 25: 439 (1973)

We have previously reported that N^6, $O^{2'}$-dibutyryl adenosine 3':5'-cyclic monophosphate (db cyclic AMP) administered intracerebroventricularly (icv) in the rat, shortened amobar bital-induced sleeping time in a dose-related manner. Five neuropharmacologic agents, which included the aliphatic hypnotics chloral hydrate and paraldehyde, the tranquilizer diazepan, the phencyclidine derivative ketamine, and the inhalation agent halothane, were also tested. Dbcyclic AMP shortened, in a dose-related manner, the duration of narcosis of each of the structurally unrelated central nervous system depressants. The purpose of the present research was to determine if db cyclic AMP administered icv protected rats treated with a toxic dose, of each of these drugs. Male Sprague-Dawley rats weighing 80-100 g were weighed and one of the central nervous system depressants was injected ip according to the following dose schedules: amobarbital. 175 mg/kg; chloral hydrate (Noctec), 500 mg/kg (diluted 1:1 in sterile saline). diazepam, 70 mg/kg, and paraldehyde, 1.5 ml/kg. Immediately after the loss of righting reflex 225 mu-g of cyclic AMP in 15 mu-l of 0. 001 m potassium phosphate buffer solution, pH 7.5, was administered icv. Our data showed that db cyclic AMP significantly reduced the mortality of amobarbital from LD50 to LD3, chloral hydrate from LD50 to LD17, and paraldehyde from LD67 to LD17. Repetitive icv doses of db cyclic AMP were required to decrease the mortality due to ketamine and diazepam. Whereas higher doses of db cyclic AMP (300 mu-g) given to rats treated with toxic doses of diazepam and ketamine resulted in shortening of the sleeping time, no reduction of the LD50 was observed. Analeptic drugs (methamphetamine, picrotoxin, doxapram, caffeine, theophylline. and strychnine) administered icv did not shorten the sleeping time or reduce the mortality of any of the central nervous system depressants used in this study.

COHN. M.L. The influence on amobarbital-induced sleeping time in rats by drugs affecting cyclic AMP. Prostaglandins and Cyclic AMP. Biological Actions and Clinical Applications. Edited by R.H. Kahn and W.E. M. Lands. New York: Academic Press, 1971. Pp. 73-74.

In previous studies we have shown that dibutyryl cyclic AMP in pharmacologic doses administered intracerebroventricularly (ICV) shortened amobarbital-induced sleeping time in a dose-related manner in rats. The duration of narcosis of structurally different anesthetic and tranquilizer agents (chloral hydrate, diazepam, paraldehyde, ketamine and halothane) was also shortened in a dose-related manner by the ICV administration of db cyclic AMP These studies suggested that cyclic AMP in vivo has a regulatory action on the duration of narcosis.

The purpose of this research was to determine the effects on the duration of amobarbital-induced narcosis by the ICV administration of neuropharmacologic agents known to increase levels of cyclic AMP in the brain.

COHN, M.L. and COHN, M. Antianesthetic effects of cyclic AMP and analeptic drugs as determined by reversal of amobarbital-induced narcosis. Proceedings of the Society for Toxicology, Washington, D.C., March 10-14, 1974.

COHN, M.L. and COHN, M. "Barrel rotation" induced by intracerebroventricular injection of somatostatin in the nonlesioned rat. Proceedings of the American Society of Pharmacology and Experimental Therapeutics, Atlantic City, New Jersey, April 13-18. 1975.

COHN, M.L. and COHN, M. Phentolamine - an antagonist of cyclic AMP regulation of narcosis. Proceedings of the Society for Neurosciences, San Diego, California, November 7-10, 1973.

COHN, M.L. and COHN, M. The role of thyrotropin releasing factor and cyclic AMP in the duration of amobarbital-induced narcosis. Proceedings of the Society for Neurosciences, St. Louis, Missouri, October 20-23, 1974.

COHN, M.L. and COHN, M. Thermoregulatory control in the rat anesthetized with amobarbital. Role of thyrotropin releasing factor. Proceedings of the American Society of Anesthesiologists, Washington, D.C., October 12-16, 1974.

COHN, M.L., COHN, M. and TAYLOR, F.H. Norepinephrine - an antagonist of dibutyryl cyclic AMP in the regulation of narcosis in the rat. Research Communications in Chemical Pathology and Pharmacology 7: 687-699 (1974)

Norepinephrine (NE) (25-300 mu-g) administered centrally to rats anesthetized with amobarbital prolonged narcosis. The higher doses of NE (150-300 mu-g/rat) induced severe toxic symptoms followed by death. The addition of varying doses of dibutyryl adenosine 3', 5'-monophosphate (db cyclic AMP) to NE (150 mu-g) reduced the duration of narcosis potentiated by the latter but did not alter the toxic symptoms of the higher doses. In the regulation of the duration of narcosis, the lack of analogy between the behavioral effects of exogenously administered NE and db cyclic AMP challenges the concept that the action of NE is mediated in the brain uniquely through a second messenger system.

COHN, M.L., KRAYNACK, B., COHN, M. and SCATTAREGIA, F. Interaction of cyclic AMP with neuropharmacologic depressant agents. Federation Proceedings 32:680 (1973)

The purpose of this study was to determine which categories of CNS depressant were antagonized by db cyclic AMP (db CAMP). Previous findings showed that dibutyryl surrogate of cyclic AMP administered intracerebroventricularly (ICV) regulated in a dose-related manner the duration of amobarbital-induced narcosis (Neuropharm. in press). Structurally different neuropharmacologic depressant agents (the aliphatic hypnotics, chloral hydrate and paraldehyde, the tranquilizer, diazepam, the phencyclidine derivative, ketamine, and the inhalation agent, halothane) were similarly antagonized. Sprague-Dawley male rats weighing 80-125 g were given intraperitoneal injections of one of the CNS depressant agents in the following dose schedule: ethanol 4.86 g/kg; methanol 11.34 g/kg; meperidine 80 mg/kg; lidocaine 160 mg/kg. Each rat was given an ICV injection of db CAMP in varying concentrations (90 mu-g to 225 mu-g). Ethanol and methanol sleeping time and overdosage were antagonized in a manner similar to amobarbital. In contrast, the ICV administration of db CAMP to meperidine and lidocaine-treated rats augmented the toxic effects and increased the mortality. The data suggests that there are two general groups of neuropharmacologic CNS depressant agents. They may be classified according to their response to exogenously administered db CAMP. Further work is necessary to explain the diametrically different actions of db CAMP.

COHN, M.L., TAYLOR, F., COHN M. and YAMAOKA, H. Dibutyryl cyclic AMP - an effective antidote against lethal amounts of amobarbital in the rat. Research Communications in Chemical Pathology and Pharmacology 6: 435-446 (1973)

Dibutyryl cyclic AMP is a potent antianesthetic agent to amobarbital-induced narcosis in the rat. Our evidence demonstrates that without other supportive therapy centrally administered dibutyryl cyclic AMP also reverses barbiturate poisoning by selectively antagonizing barbiturate-induced depression without producing generalized stimulation. Such findings suggest the properties of a true antidote to the barbiturate. Furthermore, reversal of overdosage is not limited to barbiturates; dibutyryl cyclic AMP seems to reverse toxic levels of all central nervous system depressants that induce narcosis.

COHN. M.L., YAMAOKA, H., TAYLOR, F.H. and KARYNACK, B. Action of intracerebroventricular dibutyryl cyclic AMP on amobarbital anesthesia in rats Neuropharmacology 12: 481-495 (1973).

The ability of intracerebroventricular exogenous administration of N^6,$O^{2'}$-dibutyryl analog of adenosine 3':5'-cyclic monophosphate (db clycic AMP) to shorten the duration of amobarbital anaesthesia in a dose-related manner has been shown in the rat. Alteration of the duration of sleeping time (ST) appeared to be specific to db cyclic AMP since neither adenosine nor guanosine nucleotides administered intracerebroventricularly produced any appreciable effects. Similarly, intracerebroventricular injected succinate or pyruvate did not alter amobarbital-induced ST. None of the behavioral symptoms observed following the intracerebroventricular injection of db cyclic AMP in the unanaesthetized conscious rat were evident in the amobarbital-anaesthetized rat.

COHN R.A., BARRATT, E.S. and PIRCH, J.H. Marijuana responses in rats: Influence of castration or testosterone. Proceedings of the Society for Experimental Biology and Medicine 146: 109-113 (1974)

Female rats show a significantly greater behavioral response than male rats to marijuana extract. This difference in response was partially aboiished through castration of males or testosterone pretreatment of females. Since castration and testosterone pretreatment may affect drug metabolism, we also studied the effects of liver microsomal enzyme induction and inhibition on responses of rats to marijuana. While enzyme inhibition increased the responses of rats to marijuana, enzyme induction did not alter behavioral responses to marijuana.

COLASANTI, B. and KHAZAN, N. Agonistic properties of narcotic analgesics and antagonists on the electroencephalogram and behavior in the rat and their reversal by naloxone. Neuropharmacology 12: 619-627 (19.73)

Adult female Sprague-Dawley rats were prepared with chronic cortical and temporalis muscle electrodes for recording of the electroencephalogram (EEG) and the electromyogram (EMG). Acute i.p. administration of the narcotic analgesics morphine. methadone, meperidine, or codeine was followed by the induction of high-voltage slow activity in the EEG during behavioral stupor of the rat, the duration of which was dose-related. Administration of the narcotic antagonists nalorphine, pentazocine, or cyclazocine resulted in similar EEG and behavioral changes. This initial period of EEG slow activity and behavioral stupor was uniformly succeeded by a secondary phase of EEG desynchrony and behavioral arousal, the duration of which depended upon the individual narcotic and antagonist agents. The narcotic antagonist naloxone, however, was devoid of such effects. Nalorphine administered at the dose ratios of 1 : 4 or 1 : 8 five min before morphine significantly reduced the duration of the morphine response. Administration of naloxone at a dose ratio of 1 : 5 five min before morphine, however, resulted in a complete reversal of the entire morphine effect. These results suggest that the induction of EEG slow activity in association with stuporous behavior of the rat is an agonistic property of narcotics and antagonist-analgesics which is reversed by “pure” narcotic antagonists.

COLASANTI, B. and KHAZAN, N. Antagonism of the acute electroencephalographic and behavioral effects of morphine in the rat by depletion of brain biogenic amines. Neuropharmacology 12: 463-469 (1973)

Adult female Sprague-Dawley rats were prepared with chronically implanted cortical and temporalis muscle electrodes for recording of the electroencephalogram (EEG) and the electromyogram (EMG). Morphine injections of 10 mg/kg given i.p. to saline-treated rats were followed almost immediately by the appearance of high voltage EEG slow bursts associated with stuporous behavior, which prevailed for 60-90 min. This phase was superseded by the prevalence of EEG and behavioral arousal over an additional period of 60-90 min. after which EEG and behavioral sleep appeared. Administration of a 10 mg/kg dose of morphine to rats pretreated with (±)-alpha-methyl-para-tyrosine (alpha-MPT) was followed by a slight but significant shortening of the period of EEG slow bursts and the behavioral stupor as well as by a reduction in the duration of the entire morphine effect. In contrast, rats pretreated with para-chlorophenylalanine (p-CPA) responded to morphine by an almost immediate and continuous EEG and behavioral arousal, with only a few intervening episodes of behavioral stupor associated with EEG slow bursts. This effect of p-CPA was completely reversed by the administration of 5-hydroxytryptophan (5-HTP) prior to the morphine injection. Pretreatment of the rats with both p-CPA and alpha-MPT likewise resulted in an attenuation of the period of morphine-induced EEG and behavioral stupor concomitant with a prolongation of the period of behavioral arousal. The effects of this treatment, however, were less pronounced than those occurring after p-CPA alone. These results suggest that the relative amounts of all three monoamines norepinephrine, dopamine, and 5-hydroxytryptamine in the brain, rather than the absolute levels of any one amine, are important in the mediation of the central effects of morphine.

COLASANTI, B. and KHAZAN, N. Changes in EEG voltage output of the sleep-awake cycle in response to tetrahydrocannabinols in the rat. The Pharmacologist 12: 246 (1971)

Marihuana and the active delta-8- and delta-9-trans-tetrahydrocannabinol (delta-8-and delta-9-THC) derivatives are generally regarded as psychotomimetics with sedative properties. Since the sympathomimetic hallucinogens have been reported to cause a reduction in the mean voltage output of the EEG and its coefficient of variation, the present study was undertaken to determine whether a similar change would follow the administration of THC. Adult female Sprague-Dawley rats with chronic cortical and temporal muscle electrodes were used. Administration of delta-8-THC i.p. at doses ranging from 2.5 to 10.0 mg/kg was followed by a dose-related decrease in the voltage output of the awake state EEG. The Bleep and REM sleep states were relatively less affected. Polyspike discharges, reported previously to occur after the administration of marihuana extract of delta-8-THC (Masur and Khazan, Life Sci. 9:1275, 1970), were superimposed on the low voltage EEG awake tracings. Administration of delta-9-THC resulted in similar EEG changes. The reduction in the voltage output of the EEG in conjunction with the occurrence of the polyspike discharges, unique to this group of psychotomimetics, is presumed to correlate with a state of CNS arousal during which the rat appears behaviorally sedated.

COLASANTI, B. and KHAZAN, N. Effects of delta-8-tetrahydrocannabinol on the voltage output of the EEG in the rat. Committee on the Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council, 1971.

COLASANTI, B. and KHAZAN, N. Imipramine-induced changes in the rapid eye movement sleep rebound and wet dog shakes of morphine-abstinent rats. Neuropharmacology (in press)

COLASANTI, B. and KHAZAN, N. Interactions of narcotic analgesics and antagonists on the electroencephalogram (EEG) and behavior of the rat. Federation Proceedings 31: 304 (1972)

The induction by morphine of high voltage EEG slow bursts has been reported to occur both in experimental animals and in man. The present study has been undertaken to explore the specificity of this effect in relation to other narcotic analgesics as well as the narcotic antagonists. Adult female Sprague-Dawley rats were prepared with chronic cortical and temporalis muscle electrodes. Acute i.p. injection of the narcotic analgesics morphine, methadone, meperidine. and codeine was followed by the induction of high voltage slow activity in the EEG. The appearance of EEG slow bursts was accompanied by stuporous behavior of the rat. These effects were dose-related and paralleled the relative potencies of the narcotic agents. The narcotic antagonists nalorphine and naloxone, administered i.p., were effective in blocking the appearance of slow bursts in the EEG. Administration of nalorphine alone, however, was followed by similar EEG changes. These results suggest that the induction of EEG slow bursts in association with stuporous behavior of the rat is an agonistic property of narcotics and antagonist-analgesics which is blocked by narcotic antagonists.

COLLINS, P.I., WEI, E. and WAY, E.L. The central site of morphine analgesia in rats. Proceedings of the Western Pharmacological Society 17: 164-167 (1974).

COLLINS, P.I., WEI, E. and WAY, E.L. Central sites of morphine analgesia. Proceedings of the Western Pharmacological Society 17: 164 (1974)

No chemical agent has yet been developed which surpasses morphine or morphine-like drugs in the clinical relief of pain; An understanding of the sites and mechanisms underlying the antinociceptive action of morphine may therefore be useful in developing new approaches to pain relief. The central sites of morphine analagesia have been ascribed to the areas surrounding the third (1) and fourth ventricle (2), the periventricular and periaqueductal grey of the brain stem (3), the anterior medial thalamus (4) and the posterior hypothalamus (5). In this investigation, we determined the brain areas where localized application of crystalline naloxine, an opioid antagonist, reversed the analgesia induced by morphine administered systemically.

COCK, J.D. and SCHANBERG, S.M. The effects of methamphetamine on behavior and on the uptake, release and metabolism of norepinephrine. Biochemical Pharmacology 19: 1165-1179 (1970)

The use of different dose-response schedules may be responsible for conflicting reports between changes in behavior and norepinephrine metabolism in brain following the administration of amphetamine. Therefore, the effects of methamphetamine on the levels of endogenous norepinephrine and on the metabolism of tritiated (^{3}H) norepinephrine in brain were studied after different dose regimens and post. medication intervals. Various time intervals after the intraperitoneal injection of methamphetamine (5 mg/kg) norepinephrine-^{3}H was injected into the criteria magna of rats. Five min later, the brains were removed and assayed for endogenous norepinephrine, tritiated norepinephrine and its metabolites (normetanephrine, deaminated catechols and Ω-methylated deaminated catechols). Uptake of norepinephrine-^{3}H was inhibited at 0.5 and 1•0 hr, returned to control levels at 2 hr and exceeded these levels at 5 hr. Both tritiated deaminated catechol and Ω-methylated deaminated metabolite levels were decreased at 0•5 and 1 hr but approached control levels when determined 5 hr post methamphetamine administration. Normeta'nephrine- ^{3}H levels were highest (220 per cent of control) at 0•5 hr, then decreased at each successive test time to 130 percent control level at 7 hr. Endogenous levels of norepinephrine were increased for the first hour and then fell to 85 per cent of control levels at 3 hr. When norepinephrine-^{3}H was injected prior to methamphetamine administration, no significant release of the labeled amine occurred until 7 hr after the administration of the drug. In these release studies, as was seen in the uptake studies, decreased levels of deaminated catechol-^{3}H and increased normetanephrine-^{3}H levels occurred although norepinephrine-^{3}H levels were not significantly lowered. This supports the hypothesis that methamphetamine interferes with the deamination of norepinephrine by monoamine oxidase. Changes in behavioral ratings had a time course similar to alterations in norepinephrine-^{3}H uptake and metabolism. A high correlation was found between the changes in behavior and normetanephrine-^{3}H levels.

It is clear from these data that to properly evaluate interrelationships between drug effects on metabolism and behavior, it is essential to compare several dose-response schedules rather than using a single arbitrary regimen.

COOPER, B.R. and BREESE, G.R. Relationship of dopamine neural systems to the behavioral alterations produced by 6-hydroxydopamine administration into brain. Neuropsychopharmacology of Monoamines and Their Regulatory Enzymes. Edited by E. Usdin. New York: Raven Press, 1974.

COOPER, B.R., COTT, J.M. and BREESE, G.R. Effects of catecholamine-depleting drugs and amphetamine on self-stimulation of brain following various 6-hydroxydopamine treatments. Psychopharmacologia 37: 235-248 (1974)

Changes in electrical self-stimulation responding were examined in rats with electrodes implanted in the lateral hypothalamus following 6-hydroxydopamine treatments which depleted brain dopamine, norepinephrine or both of these catecholamines. Acute depression of self-stimulation occurred after treatments which reduced brain dopamine, but did not occur in rats treated to deplete just brain norepinephrine. A chronic deficit in self-stimulation responding occurred in rats treated with 6-hydroxydopamine in combination with pargyline to reduce both brain amines, while responding of animals in which brain dopsmine was reduced returned to levels observed prior to 6-hydroxydopamine treatment. A dose of alpha-methyltyrosine (25 mg/kg), which did not affect responding of control rats, caused a significant reduction in responding of rats depleted of brain dopamine. This treatment did not affect responding of rats depleted of brain norepinephrine. Administration of the dopamine-beta-hydroxylase inhibitor, U-14624, failed to affect self-stimulation in spite of an additional 70%

Cooper, B.R., Cott, J.M. and Breese, G.R. continued
reduction of brain norepinephrine content. The response to a dose of d-amphetamine (0.25 mg/kg), that increased self-stimulation of control rats, was significantly reduced in rats with brain dopamine selectively depleted. Rats in which norepinephrine was depleted responded to d-amphetamine like the control group. Alpha-methyltyrosine antagonized the increased self-stimulation responding following administration of d-amphetamine (1 mg/kgl to reserpinized rats, while U-14624 did not. Results support the hypothesis that central dopaminergie fibers have an important involvement in the maintenance of self-stimulation of brain.

COUSENS, K. and DiMASCIO, A. (-)-Delta-9-THC as an hypnotic. Psychopharmacologia 33: 355-364 (1973)

(-)-Delta-9-THC was found to significantly decrease the time it takes to fall asleep in physically healthy insomniacs. Once asleep, interruptions of sleep were not significantly altered over the whole night. The (-)-delta-9-THC tended to be associated with some decrease in awakenings in the first half of the night.

The primary side effect experienced by the subjects at all dose levels in the Pre-Sleep phase was temporal disorganization and mood alterations. There was an increase in intensity of side effects and number of subjects affected with increasing dosage.

The most significant side effect, however, was a "hangover" phenomenon, or continued "high" the next day, with some residual of temporal disorganization. It increased in intensity and duration with increase in dosage. This "hangover" seems severe enough to eliminate the consideration of the 30 mg dose range, of (-)-delta-9-THC for clinical use as an hypnotic.

CROFFORD, M. and SMITH, A.A. Growth retardation in young mice treated with dl-methadone. Science 181: 947-949 (September, 1973)

Newborn mice injected daily for 6 weeks with dl-methadone in dosages of 2 to 8 milligrams per 'kilogram grew significantly more slowly than their saline-treated littermates. Litters given d-methadone, 4 milligrams per kilogram, grew normally. Concomitant treatment with naloxone, 10 milligrams per kilogram, prevented growth inhibition. A weight deficit persisted in mice observed 6 weeks after cessation of methadone treatment.

CROMBIE, L., PONSFORD, R., SHANI, A., YAGNITINSKY, B. and MECHOULAM, R. Photochemical production of cannabicyclol from cannabichromene. Tetrahedron Letters 55: 5771-5772 (1968)

CROWDER, W.F., SMITH, S.G., DAVIS, W.M., NOEL, J.T. and COUSSENS, W.R. Effect of morphine dose size on the conditioned reinforcing potency of stimuli paired with morphine. The Psychological Record 22: 441-448 (1972)

After an initial operant level period, 22 rats were given non-contingent pairing of a buzzer with intravenous injections of morphine solution in doses of 0.0032 mg/kg, and 0.032mg/kg. The buzzer plus a saline infusion were then presented contingently on bar-pressing behavior. The results of this test indicated that buzzer plus saline infusion had acquired secondary reinforcing properties, the magnitude of which increased with increasing dosage of morphine. The results may be attributed to conditioned positive reinforcement, since no physical dependence was evident. The present findings also suggest that a stimulus can become a secondary reinforcer without being a discriminative stimulus for an operant.

CUMMINS, J.T. and MORIN, A.M. The effect of reserpine and morphine on the release of endogenous primary amines from isolated brain tissues. Proceedings of the Western Pharmacological Society (in press)

CUSHMAN, P., JR. Growth hormone in narcotic addition. Journal of Clinical Endocrinology 35: 352 (1972)

Growth hormone (GH) levels were measured in normals, methadone-treated, former heroin addicts and actively addicted male patients during and after insulin hypoglycemia. Normal GH response to adequate hypoglycemia was observed in the controls and the abstinent former addicts. Although most heroin-addicted and methadone-maintained patients also responded normally, some in each category had suboptimal responses. Some of these GH hyporesponders also had subnormal cortisol responses to hypoglycemia. Serum LH, T-4, T-3 and PBI's usually were normal in both heroin addicted and methadone maintained patients regardless of the magnitude of their GH responses. There was no correlation of GH responsiveness with duration of addiction. daily average cost of addiction, dose of methadone or duration. of methadone maintenance. There were no clinical stigmata of hypopituitarism in any patient. The evidence suggests a mild subtle hypothalamic-pituitary dysfunction may be present in some patients characterized principally by subnormal GH and cortisol responses to insulin hypoglycemia.

CUSHMAN, P., JR. Persistent increased immunoglobulin M in treated narcotic addiction. Journal of Allergy and Clinical Immunology 52(2): 122-128 (August, 1973)

The increased serum IgM in treated narcotic addiction was studied using quantitative radial diffusion techniques. Seventy per cent of 68 untreated heroin addicts had serum IgM levels above 280 mg. per deciliter, the upper limit of normal. Only 7 per cent of 15 abstinent patients had high serum IgM, while 36 or 33 per cent of 109 patients maintained on methadone for at least one year had high serum IgM levels. Fourteen of these 36 had known heroin use and 10 others abused other drugs including alcohol, whereas only 2 of the 73 methadone-maintained patients with normal serum IgM had known drug abuse. The association between positive urine spots for morphine and elevated serum IgM levels was significant (p less than 0.01). There was a significant relationship between laboratory evidence of liver disease and increased serum IgM levels. Increased serum alkaline phosphate correlated better (p less than 0.01) than the serum glutamic oxaloacetic transaminase (SCOT) (p less than 0. 05) with high serum IgM levels in methadone-maintained patients, High serum IgM levels in treated addicts are associated with continuing drug abuse and/or with laboratory evidence of continuing mild liver disease.

CUSHMAN, P., JR. and KREEK, J.J. Some endocrinologic observations in narcotic addicts. Narcotics and the Hypothalamus. Edited by E. Zimmermann and R. George. New York: Raven Press, 1974.

DAVIS, J.M., JANOWSKY, D.S., EL-YOUSEF, M.K., and SEKERKE. H.J. Drug Interactions Involving Drugs of Abuse. Washington, D.C.: U.S. Government Printing Office, 1973.

DAVIS, M. and SHEARD, M.H. Biphasic dose-response effects of n-n-dimethyltryptamine on the rat startle reflex. Pharmacology, Biochemistry and Behavior 2: 827-829 (1974)

The startle reflex was measured in 4 groups of 10 rats each after intraperitoneal injection of saline or 0.12. 0.25, 0. 50 or 4. 00 mg/kg N-N-dimethyltryptamine (DMT). Low doses (0.25 and 0.50) of DMT augmented startle but the high dose (4.0) depressed startle. This biphasic dose-response relationship is consistent with the hypothesis that startle is enhanced when midbrain raphe neurons are inhibited but depressed when cells post-synaptic to raphe neurons are also inhibited.

DAVIS, M. and SHEARD, M.H. Effects of lysergic acid diethylamide (LSD) on habituation and sensitization of the startle response in the rat. Pharmacology, Biochemistry and Behavior 2: 675 (1974)

In 4 experiments the effect of d-lysergic acid diethylamide (LSD) on the acoustic startle response in rats was measured. A low dose (20 mu-g/kg) facilitated startle but a high dose (160 mu-g/kg) at first facilitated but then depressed startle somewhat relative to an intermediate dose (40 mu-g/kg). 2-brom LSD (199 mu-g/kg) had no detectable effect and 40 mu-g/kg LSD did not change startle in raphe-lesioned rats. LSD appeared to augment sensitization rather than acting on the startle circuit directly since it did not increase startle unless given in conjunction with either background noise or repetitive tones. LSD did not prevent between session habituation. Relationships between habituation, sensitization, and the midbrain raphe nuclei were discussed.

DAVIS, P.W. and HORITA, A. Chronotropic responses to catecholamines as a function of monoamine oxidase activity in the isolated perfused rat heart. Archives internationales de Pharmacodynamie et de Therapie 173(2): 386 (June, 1968).

There has been considerable recent interest in the possible role of monoamine oxidase (MAO) in the termination of pharmacological responses to exogenously administered catecholamines and agents which act indirectly by the release of norepinephrine. The purpose of the present study was to investigate the chronotropic responses to catecholamines as a possible function of MAO activity in the isolated perfused rat heart. Dopamine, a directly-acting amine and good MAO substrate, and alpha-methyldopamine, a directly- and indirectly-acting amine and non-substrate for MAO, were selected for study.

DAVIS, V.E., CASHAW, J.L., McLAUGHLIN, B.R. and HAMLIN, T.A. Alteration of norepinephrine metabolism by barbiturates. Biochemical Pharmacology 23: 1877-1889 (1974)

Competitive inhibition of NAD-linked aldehyde dehydrogenase by acetaldehyde, the primary metabolite of ethanol, enhances the formation in vitro of tetrahydropapaveroline (THP), a tetrahydroisoquinoline (THIQ) alkaloid derived from the condensation of dopamine (DA) with 3,4-dihydroxyphenylacetaldehyde. Unlike the DA-derived aldehyde, the aldehyde derivative of norepinephrine (NE) is not appreciably oxidized in brain tissue to the corresponding acid by brain aldehyde dehydrogenase, but is primarily reduced to the glycol, 3,4-dihydroxyphenylglycol (DHPG), by an NADPH-dependent aldehyde reductase. Since it has been demonstrated that this partially purified aldehyde reductase from bovine brain is inhibited by barbiturates, an investigation was conducted to define the effects of barbiturates on the over-all metabolism of ^{14}C-NE and its aldehyde by rat brainstem homogenates. In the absence of exogenous NAD or NADPH, the major metabolite of deaminated NE was found in a fraction that would contain the THIQ alkaloids. A smaller portion of the deaminated NE was isolated as the DHPG and the 3,4-dihydroxymandelic acid (DHMA) metabolites. A substantial amount of the deaminated NE was also accounted for as the free aldehyde. Adding NADPH markedly increased DHPG formation while decreasing alkaloid synthesis. Incorporating barbiturates into incubation mixtures containing NADPH. or a mixture of NAD and NADPH. appreciably inhibited DHPG production, thereby enhancing free glycolaldehyde levels and augmenting alkaloid formation. Thus, barbiturates - like ethanol, as mediated by acetaldehyde - markedly modify neuroamine-derived aldehyde metabolism.

DAVIS, W.M., BABBINI, M., COUSSENS, W.R., SMITH, S.G. and CROWDER, W.F. Antagonism of behavioral effects of morphine by alpha-methyltyrosine (AMT). The Pharmacologist 13(2): 280 (1971)

Many studies have attempted to relate brain catecholamines and/or serotonin to the analgesic action and to the mechanisms of tolerance and physical dependence associated with morphine sulfate (MS). Other actions of MS have been little investigated in this regard. We used 50 mg/kg (i.p.) doses of 1-AMT given 4-5 hr. prior to the expected peak of MS effect on locomotor activity of the rat. The immediate enhancement of motility following 5.0 mg/kg (i.p.) MS, and the delayed stimulation after 20 mg/kg both were blocked. Also, the enhanced stimulatory response to 10, 20, or 40 mg/kg MS after daily administration for 18 days was suppressed by AMT pretreatment on day 19. Bar-pressing which delivered 0.32 mg/kg doses of MS via a chronic indwelling jugular catheter on a CRF schedule was quickly elevated above operant response levels (many rats pressing several hundred times on 1st day). Such self-injection behavior also was suppressed by 50 mg/kg i.p. dl-AMT. Thus, it appears that both behaviors are dependent upon the functional pool of brain catecholamines.

DAVIS, W.M., BABBINI, M. and KHALSA, J.H. Antagonism by alpha-methyltyrosine of morphine induced motility in non-tolerant and tolerant rats. Research Communications in Chemical Pathology and Pharmacology 4(2): 267-279 (1972)

The immediate locomotor stimulation induced by a 5.0 mg/kg i.p. dose of morphine sulfate, and the delayed stimulation after a 20 mg/kg dose both were blocked by pretreatment with 50 mg/kg (i.p.) of L-alpha-methyl-p-tyrosine (AMT). Similarly, the enhanced locomotor response to 10. 20 and 40 mg/kg doses of morphine after their daily administration for 18 days was antagonized by AMT pretreatment given on the 19th day. AMT had little or no effect on activity levels in control groups receiving no morphine, but it reduced brain catecholamine levels by about 50% at the time of activity testing. Pretreatment with L-DOPA (160 mg/kg) alone did not reverse the effect of AMT. but the morphine effect was restored by L-DOPA plus reserpine (3.2 mg/kg). It is evident that morphine-induced locomotor stimulation was dependent upon normal availability of brain catecholamines.

DAVIS, W.M. and BORGEN, L.A. Tolerance development to the effects of delta-9-THC on conditioned behavior: Role of treatment interval and influence of microsomal metabolism. Archives internationaIes de Pharmacodynamie et de Therapie (in press)

DAVIS, W.M. and KHALSA, J.H. Morphine lethality in rats: Effects of inhibitors of brain catecholamine synthesis and methylation. Research Communications in Chemical Pathology and Pharmacology 6(3): 867-872 (1973)

Tropolone, an inhibitor of catecholamine-O-methyltransferase, alpha-methyltyrosine (AMT), an inhibitor of tyrosine hydroxylase, and U-14,624, an inhibitor of dopamine-beta-hydroxylase were tested for an ability to alter the acute lethal toxicity of morphine sulfate. Tropolone (50 mg/kg. i.p.) reduced the 24-hr i.p. LD50 of morphine in male Holtzman rats from 292 to 54 mg/kg. The other two agents both elevated the LD50 significantly. It is suggested that the potentiation of morphine by tropolone resulted from a reduced inactivation of brain catecholamines released by the action of morphine, while the protection afforded by AMT and U-14,624 pretreatment was a result of their inhibition of brain catecholamine synthesis.

DAVIS, W.M. and KHALSA, J.H. Some determinants of aggressive behavior induced by morphine withdrawal. Psychonomic Science 24(1): 13-15 (1971)

Male and female rats of Sprague-Dawley and Long Evans strains were given daily intraperitoneal injections of morphine sulfate in increasing dosages over a 15-day period to a terminal dose of 405 mg/kg/day. During withdrawal, fighting behavior occurred equally among older male rats (60 days at start of experiment) of both strains, housed in groups of six, but not at all in younger ones (30 days). A strain difference found earlier in 45-day-old rats was confirmed. Females of either strain or age, showed no aggressive behavior during withdrawal. Decreasing available cage space increased the number of aggressive encounters, despite a reduction of group size to four. Saline-injected males of either strain rarely displayed aggression. A circadian rhythmicity of such behavior was not found. There was evidence for a seasonal variation in frequency of morphene-withdrawal-induced aggression, levels being higher in summer than in winter.

DAVIS, W.M., LOGSTON, D.G. and HICKENBOTTOM, J.P. Antagonism of acute amphetamine intoxication by hatoperidol and propranolol. Toxicology and Applied Pharmacology 29: 397-403 (1974)

The antidotal effects of a butyrophenone neuroleptic, haloperidol (HAL), and a beta-adrenergic blocking agent, propranolol HCl(PRO), against the acute toxicity of d -amphetamine sulfate (AS) were determined. Alteration by such treatments of 2 biochemical changes implicated in the lethal mechanism(s) of AS also 'were examined. Male Sprague-Dawley rats (130-160 g) were injected ip with 64.8 mg/kg (1.5 x LD50) of AS. At 5 or 15 min after AS, SC injections of either PRO (10 or 20 mg/kg), HAL (0. 5 or 1.0 mg/kg), or a combination of PRO (20) and HAL (1.0) were given. Both doses of PRO and of HAL afforded considerable protection against AS lethality compared to saline posttreated controls. However, the combination did not protect as well as did the more effective single agent, HAL. Hypoglycemia at 25 min after AS was prevented only by HAL (0.5 mg/kg) injection at 15 min post-AS. The 4-6-fold elevation of plasma lactate at 25 min after AS was prevented by posttreatment with PRO (20 mg/kg), but not by the HAL doses, which greatly reduced lethality. The data do not indicate that prevention of these biochemical effects of AS was critical to reduction of mortality. It is suggested that HAL and PRO deserve consideration as useful alternative or supplemental antidotes to those presently recommended for human acute intoxications from amphetamine-like drugs.

DAVIS, W.M. and SMITH, S.G. Alpha-methyltyrosine to prevent self-administration of morphine and amphetamine. Current Therapeutic Research 14(12): 814-819 (1972)

Rats equipped with jugular cannulas were given opportunity to self-administer intravenous doses of morphine sulfate (32 mcg/kg) or d-amphetamine sulfate (15 mcg/-kg) by means of a bar-press response which activated an injection device. Pretreatment with L-alpha-methyltyrosine (3 intraperitoneal doses of 75 mg/kg during an 8 hr. period prior to the experimental session) blocked the development of self-administration behavior toward both drugs. This result is interpreted as a blockade of the mechanism by which these agents act as primary positive reinforcers. Because of this property, it is suggested that alpha-methyltyrosine may be applicable in procedures designed to produce extinction of drug-seeking behavior in persons abusihg opiates and/or amphetamine.

DAVIS, W.M. and SMITH, S.G. Blocking effect of alpha-methyltyrosine on amphetamine based reinforcement. Journal of Pharmacy and Pharmacology 25: 174 (1973).

DAVIS, W.M. and SMITH, S.G. Blocking of morphine based reinforcement by alpha-methyltyrosine. Life Sciences 12: 185-191 (1973)

L-alpha-methyl-p-tyrosine (AMT) was tested for its ability to block the reinforcing action of intravenous doses (32 mu-g/kg) of morphine sulfate in non-dependent, non-tolerant rats. Three intraperitoneal doses of 75 mg/kg of AMT over 8 hours preceding an acquisition test blocked the development of self-administration behavior. The same pretreatment before a session of 100 behaviorally non-contingent pairings of a buzzer and morphine prevented the establishment of the buzzer as a conditioned (secondary) reinforcer. Because the latter effect was shown in a test performed four days after the drug treatment, it is concluded that the results cannot be attributed to non-specific motor inhibitory properties of AMT.

DAVIS, W.M. and SMITH, S.G. Central cholinergic influence on self-administration of morphine and amphetamine. Life Sciences 16: 237-246 (1974)

Atropine and methylatropine were tested in rats for an ability to alter the reinforcing action of intravenous morphine sulfate and d-amphetamine sulfate (60 mu-kg/injection). Atropine blocked the self-administration of morphine, but methylatropine did not. Similarly, atropine but not methylatropine prevented the establishment of a conditioned reinforcer based on passive intravenous infusions of morphine. Self-administration of d-amphetamine was enhanced by atropine but not by methylatropine. The results indicate that a central cholinergic system exerts an influence on the brain mechanisms which are affected by morphine or d-amphetamine to produce positive reinforcement.

DAVIS, W.M. and SMITH, S.G. Noradrenergic basis for reinforcement associated with morphine action in nondependent rats. Clinical Toxicology 7: 265 (1974)

DAVIS, W.M. and SMITH, S.G. Noradrenergic basis for reinforcement associated with morphine action in non-dependent rats. Drug Addiction: Neurobiology and Influences on Behavior, Vol. 3. Edited by J. M. Singh and H. Lal. New York: Stratton Intercontinental Medical Book Company, 1974. Pp. 155-168.

DAVIS, W.M. and SMITH, S.G. Positive reinforcing effects of apomorphine, d-amphetamine and morphine: Interaction with haloperidol. The Pharmacologist 16(2): 16 (1974)

Positive reinforcement after small i. v. doses of apomorphine HCl (APO), d-amphetamine sulfate (AS), or morphine sulfate (MS) was demonstrated both by self-administration (SA) behavior and by the establishment of a buzzer stimulus as a conditioned reinforcer through pairings of buzzer and drug infusions (as per Davis & Smith, Life Sci. 12:185, 1973). Male albino rats were allowed to self-inject (SI) drug solutions during a 6-h session on a continuous reinforcement schedule. Rats so treated learned to SI APO (60 mu-g/kg) as quickly as others did to SI AS (15 mu-g/kg)or MS (60 mu-g/kg). Some rats died from overdosing with APO in the 1st test session (up to 1129 doses were taken). Others overdosed later after several days of moderate intake. Both fatal and non-fatal levels of APO intake were accompanied by pronounced stereotypic behaviors, but these were not responsible for SI. Some individuals seemed to learn to regulate their SA so that toxic properties of APO were largely avoided. The possible dopaminergic basis of SA for all 3 drugs was tested by means of i. p. haloperidol (HAL) pretreatment. Drug-associated reinforcement was prevented by HAL in the case of APO and AS, but not for MS.

DAVIS, W.M., SMITH, S. G. and CROWDER, W.F. Morphine based conditioned reinforcement. Fifth International Congress on Pharmacology, July 23-28, 1972.

Until recently only inverse relationships for magnitude of reinforcement effects have been found for self-administered drugs. With a new conditioned reinforcement technic we find a direct relationship between morphine dose and response strength. Rats were given non-contingent pairings of a buzzer (B) with IV inj. of morphine sulfate (MS) in doses of 0.0032, 0.032 or 0.32 mg/kg. The next day B and a saline infusion (SI) were presented together contingently on bar-pressing. Response levels were elevated above respective operant levels and showed a linear trend. The results show conditioned reinforcement the magnitude of which increased with dosage of MS. To test the hypothesis that the reinforcement mechanism (RM) involves a stimulatory action, pretreatment with L-alpha-methyltyrosine (AMT) or saline was given before pairing of 0.032 mg/kg MS and B. Antagonism of morphine-induced locomotor excitation by AMT was reported (Pharmacologist 13, 280, 1971). Rats were trained as above. Nine were given 3 IP injections of 75 mg/kg AMT at 4 hr. intervals, the last at 15 min. prior to MS-B pairings. Nine were given equal vol. of saline. Results of tests after the pairings were: mean total responses for AMT group of 23.6, and for the saline group of 111.1. The AMT response did not differ from operant level. These findings suggest that function of the RM was blocked by AMT, and that RM may be catecholamine based.

DEMENT W.C., ZARCONE, V.P., HODDES, E., SMYTHE, H. and CARSKADON, M. Sleep laboratory and clinical studies with flurazepam. The Benzodiazepines. Edited by S. Garattini, E. Mussini and L. 0. Randall. New York: Raven Press, 1974. Pp. 599-611.

Laboratory studies were conducted on male insomniacs to evaluate the effectiveness of flurazepam on sleep induction and maintenance and to investigate the effects of the drug on sleep stages, particularly rapid eye movement (REM) and slow wave nonrapid eye movement (NREM). Flurazepam was shown to effectively induce and maintain sleep without profoundly suppressing REM sleep.

DENEAU, G.A. Use of the monkey colony in studies of tolerance and dependence. University of Michigan Medical Center Journal 36: 212-215 (1970)

DENEAU, G.A. and WILSON, M. Evaluation of sedative-hypnotic agents for barbiturate-like physiological dependence capacity in the dog. Committee on the Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council, 1970.

DENEAU, G., YANAGITA, T. and SEEVERS, M.H: Self-administration of psychoactive substances by the monkey. Psychopharmacologia 16: 30-48 (1969)

DEVYNCK, M.A., BOQUET, P.L., FROMAGEOT, P. and SIMON, E.J. On the mode of action of levallorphan on Escherichia coli: Effects on cellular magnesium. Molecular Pharmacology 7(6): 605-610 (1971)

Inhibition of the growth of Escherichia coli by levallorphan increased in effectiveness as the medium concentration of Mg^{++} was decreased. Two molecules of levallorphan were shown to compete with 1 atom of Mg^{++}, presumably on the cell surface. Active transport of Mg^{+} was altered in the presence of the drug, and this effect could be prevented by high concentrations of Ca^{+}. Reduction of cellular Mg^{++} content in the presence of levallorphan is suggested to be one possible cause of growth inhibition.

DEWEY, W.L. The pharmacology of pentazocine. Neuroleptanesthesia 11(3): 139 (1973)

Pentazocine is an effective analgesic that is one-third as potent as morphine by most parenteral routes of administration. The drug appears to have 2 distinct advantages over morphine and most other narcotic analgesics. First, it is active when given orally, and second, it has a lower addiction potential than the other potent analgesics presently available. However, some have abused this drug and it should be prescribed with caution for the dependency prone person. Pentazocine appears to have little hematological, hepatic. or renal toxicity but depresses the respiratory system in a manner comparable to morphine at equianalgesic doses. Pentazocine has a wide range of application in relieving severe pain. It is used preoperatively and postoperatively for a number of surgical conditions and in obstetrics for the relief of pain during labor. In the field of dentistry it is used frequently in combination with nitrous oxide anesthesia to relieve pain or as a preoperative agent.

DEWEY, W.L., HARRIS, L.S., HOWES, J.F. and NUITE, J. The effect of various neurohormonal modulators on the activity of morphine and the narcotic antagonists in the tail-flick and phenyquinone tests. The Journal of Pharmacology and Experimental Therapeutics 175(2): 435 (1970)

The effect of a number of agents which alter central neurohumeral tone on the activity of morphine and the narcotic antagonists in the tail-flick and the phenylquinone tests was studied. In general, an increase in central adrenergic tone caused an increase in the activity of morphine in the tail-flick test. However, some exceptions were observed which suggest that mechanism other than changes in neuromodulator tone might be responsible for the alterations of the potency of morphine. A number of these have been investigated and were found not to be contributing factors. Drugs which decrease adrenergic tone decreased the activity of morphine in this procedure. Alterations in adrenergic tone did not affect the analgesic activity of the antagonists.

Five-hydroxy-tryptophan caused an increase in the potency of morphine in the tail-flick procedure, thus indicating a possible involvement of central serotonergic mechanisms. A correlation between adrenergic or cholinergic tone and activity in the P-phenylquinone test was not evident. The significance of these results and the resultant validity of these procedures as screens for analgesics are discussed.

DEWEY, W.L., JENKINS, J., O'ROURKE, T. and HARRIS, L.S. The effects of chronic administration of trans-delta-9-tetrahydrocannabinol on behavior and the cardiovascular system of dogs. Archives internationales de Pharmacodynamie et de Therapie 198: 118-131 (1972)

For abstract, see Section II. Drug Chemistry and Metabolism.,

DEWEY, W.L., McMILLAN, D.E., HARRIS, L.S. and TURK, R.F. Distribution of radioactivity in brain of tolerant and nontolerant pigeons treated with ^{3}H-delta-9-tetrahydrocannabinol. Biochemical Pharmacology 22: 399-405 (1973)

For abstract, see Section II. Drug Chemistry and Metabolism.

DINGLEDINE, R. and GOLDSTEIN, A. Morphine effect on neurons in the guinea pig myenteric plexus under conditions of synaptic transmission blockade. Federation Proceedings (in press)

DINGLEDINE. R., GOLDSTEIN, A. and KENDIG, J. Effects of narcotic opiates and serotonin on the electrical behavior of neurons in the guinea pig mycnteric plexus. Life Sciences 14: 2299-2303 (1974)

Action potentials were recorded extracellularly from spontaneously firing neurons in the myenteric plexus of the guinea pig ileum. Morphine, which inhibits acetylcholine release from the myenteric, plexus, inhibited the spontaneous electrical activity of about half the cells studied, while serotonin elevated the firing rate of these cells. Units not stimulated by serotonin were not inhibited by morphine or levorphanol. Morphine also prevented the increase in firing rate caused by serotonin. These effects of morphine were stercospecific and blocked by naloxone, and are therefore considered to he specific opiate effects. This study demonstrates opposing effects of narcotic opiates and serotonin on the electrical activity of serotoninoceptive neurons in the myenteric plexus.

DITMAN, K.S., MOSS, T., FORGY, E.W., ZUNIN, L.M., LYNCH, R.D. and FUNK, W.A. Dimensions of the LSD, methylphenidate and chlordiazepoxide experiences. Psychopharmacologia 14(1): 1-11 (1969)

Dimensions of the LSD, methylphcnidate and chlordiazepoxide experiences are studied. Through the retrospective use of the 156 item DWM card sort, the experiences from a single intravenous dose of 200 mg of LSD, 75 mg of methylphenidate (ritalin) and 75 mg of chlordiazepoxide (librium) were compared in a population of 99 chronic male alcoholics treated in an "LSD setting" in a double-blind study. Surprisingly, 96 of the 156 items proved significantly different among the 3 groups. LSD was unique in producing sensory and perceptual distortions (including hallucinations or illusions), and mystical, religious or paranormal sensations. However, contrary to expectation, LSD did not uniquely produce the traditional "therapeutic" experience, but appeared to be surpassed in that area by methylphenidate. Both drugs also produced some anxiety, while chlordiazepoxide produced relaxation, and enhanced music appreciation.

DOLBY, T.W. and KLEINSMITH, L.J. Effects of delta-9-tetrahydrocannabinol on the levels of cyclic adenosine 3', 5'-monophosphate in mouse brain. Biochemical Pharmacology 23: 1817-1825 (1974)

The effects of intraperitoneal injections of various doses of delta-g-tetrahydrocannabinol (delta-9-THC) on brain levels of cyclic adenosine 3', 5'-monophosphate (cyclic AMP) have been studied in mice. Doses of delta-9-THC in the range of 0.1 to 1.0 mg/kg cause a 50-160 percent elevation of cyclic AMP levels compared to controls (P less than 0. 00051, while doses of delta-9-THC in the range of 2.0 to 10.0 mg/kg cause a 30-60 percent depression of cyclic AMP levels (P = 0.025 to 0.0005). This pattern was obtained in whole brain, as well as in dissected samples of cortex, cerebellum and medulla. This over-all biphasic effect of THC on cyclic AMP levels correlates with known changes in biogenic amines, temperature regulation, and behavior caused by this drug.

DOLE, W.P. and SIMON. E.J. Effects of levorphanol on phospholipid metabolism in the giant axon of the squid. Journal of Neurochemistry 22: 183-185 (1974)

We have reported that levorphanol and other morphine type narcotic analgesics block the evoked action potential in the isolated giant axon of the squid (Simon & Rosenberg, 1970). This finding has led us to investigate the effect of levorphanol on another aspect of the membrane physiology of the squid axon, namely, the metabolism of phospholipids. The results reported here indicate that incubation of squid giant axons with levorphano! alters phospholipid metabolism at a concentration which blocks electrical conduction,

DOMINO, E.F., HUDSON, R.D. and ZOGRAFI, G. Drugs Affecting the Central Nervous System, Vol. 2. Edited by A. Burger. New York: Marcel Dekker, Inc. 1968. Pp. 327-397.

DOMINO, E. F. and WILSON, A. E. Decreased rat brain acetylcholine utilization following heroin and cross tolerance to l-methadone. Biochemical Pharmacology (in press)

DORNBUSH, R.L., CLARE, G., ZAKS, A., CROWN, P., VOLAVKA, J. and FINK, M. 21-Day administration of marijuana in male volunteers. Current Research in Marijuana. Edited by M.L. Lewis. New York: Academic Press. 1972.

DORRANCE, D.L., BEIGHLIE. D.J., YOSHII, V., JANIGER, O., BRODETSKY, A.M. and TEPLITZ, R.L. Studies on the mechanism of interactions between lysergic acid and chromoSomes. Journal of Laboratory and Clinical Medicine 84(1): 36-41 (July, 1974)

The present communication presents data on the effects of pure lysergic acid diethylamide (LSD) at varying concentrations (in vitro) upon chromosome structure and number. In addition, this study explores the effects of the drug upon the ability of cells to repair ultraviolet-damaged DNA. The latter test was based on published data indicating intercalation of LSD into the helix of DNA. Significant changes of chromosomes occurred only at high doses. Neither LSD nor drugs which bound or intercalated into DNA affected the DNA repair process.

DORRANCE, D., JANIGER. O. and TEPLITZ, R.L. In vivo effects of illicit hallucinogens on human lymphocyte chromosomes. Journal of the American Medical Association 212(9): 1488 (June, 1970)

Fourteen subjects exposed to illicit lysergic acid diethylamide (LSD) and nine exposed to marihuana were compared to age-matched controls for effects upon lymphocyte chromosomes. Eight out of 1,284 in the group given LSD, or 0.76%, exhibited chromosomal abnormalities; seven out of 816, or 0.86%, in the group given marihuana; and eight out of 1,018, or 0.79%, in the control group. Cells were grown in medium unenriched with nucleotide precursors. Thus, our negative results mitigate against medium deficiency as contributing toward positive effects. Similarly, our results on individuals whose last dosage was within an hour or so of specimen procurement indicates that this factor may not explain conflicting results.

DREW, W.G. and MILLER, L.L. Cannabis: Neural mechanisms and behavior--a theoretical review. Pharmacology 11: 12-32 (1974)

For abstract, see Section II. Drug Chemistry and Metabolism.

DREW, W.G., MILLER, L.L. and BAUGH, E.L. Effects of delta-9-THC, LSD-25 and scopolamine on continuous, spontaneous alternation in the Y-maze. Psychopharmacologia 32: 171-182 (1973)

The effects of delta-9-THC, LSD-25 and scopolamine on continuous, spontaneous alternation of the hooded rat in the Y-maze were determined. LSD and scopolamine decreased the number of arm entries (responsivity) while concomitantly reducing percent alternation. THC however, reduced responsivity and percent alternation more at the lower dose (1 mg/kg) when compared to control than at the higher dose (3 mg/kg). Only scopolamine induced a significant increase in stimulus perserveration. The results are discussed in relation to the advantages afforded by the continuous spontaneous alternation procedure.

DREW, W.G. and SLAGEL, D.E. Delta-9-THC: Selective impairment of corticosterone uptake, by limbic structures of the rat. Neuropharmacology 12: 909-914 (1973)

Delta-9-tetrahydrocannabinol (THC) has a marked influence on the selective uptake of ^{3}H-corticosterone by the hippocampus and septum of the rat. Analysis of variance on blood/tissue ratios showed that a dose of 9 mg/kg of delta-9-THC Bignificantly (Pless than 0.01) lowered ^{3}H-corticosterone uptake in the hippocampus. Compared with uptake in frontal and hind cortices, delta-9-THC selectively depressed ^{3}H-corticosterone uptake within the septum and hippocampus. The decrease in uptake across the 3 and 9 mg/kg doses for the limbic system components compared with the cortical samples is highly significant (P 1ess than 0.001) and suggests that delta-g-THC exerts differential actions on hormone uptake within the central nervous system.

DUARTE-ESCALANTE, O. and ELLINWOOD, E.H., JR. Central nervous system cytopathological changes in cats with chronic methadrine intoxication. Brain Research 21: 151-155 (1970)

DUARTE-ESCALANTE, O. and ELLINWOOD, E., JR. Depletion of biogenic amines and enhancement of cholinergic activity in the olfactory bulb and central olfactory connections with chronic methedrine intoxication. Arquivos de Neuro-Psiquiatria 28(2): 110-117 (June, 1970)

For abstract, see Section II. Drug Chemistry and Metabolism.

ECHOLS, S.T. and JEWETT, R.E. Effects of morphine on sleep in the cat. Psychopharmacologia 24:435-448 (1972)

The effects of morphine sulfate, 300 mu-g/kg s.c., on the sleep of cats was studied by electroencephalographic techniques. In contrast to placebo experiments the animals were awake for approximately 6 h after administration of morphine; the return of regular sleep patterns occurred after about 11 h. A rebound increase in rapid eye movement (REM) sleep time and percentage was noted during the 11th through the 17th hour of the study. Sleep following manual sleep deprivation for 10 h showed a rebound increase in REM and non-rapid eye movement (NREM) sleep time. NREM sleep rebound after manual sleep deprivation exceeded that occurring after morphine. The alerting actions of morphine could be blocked by naloxone, 100 mu-g/kg s.c., for about 90 min. Naloxone alone increased REM sleep time and percentage. Single (84 mg/kg) or multiple (51 mg/kg for 4 injections) doses of dl-alpha-methyltyrosine i.p. did not block the alerting action or REM sleep rebound caused by morphine. 5-Hydrotryptophan (30 mg/kg) i.p. did not antagonize the alerting action of morphine.

EHRENPREISS, S., GREENBERG, J. and COMATY, J. The ileum of chronically morphinized guinea pig develops tolerance to injected morphine. Federation Proceedings (in press)

Injection of a large dose of morphine into a guinea pig results in a block of electrically-induced contractions of the ileum in vitro. A similar dose is almost ineffective in guinea pigs given morphine chronically (Ehrenpreis, et al in "Drug Addiction: Experimental Pharmacology", Singh et al, eds., 1972 p. 319). The time course for development of this tolerance has been determined in guinea pigs injected twice daily with morphine 100 mg/kg and challenged on various days with 750 mg/kg of the drug. Animals similarly injected but not challenged served as controls. The inhibitory effect of the challenging dose on electrical stimulation of longitudinal muscle decreased with successive days of morphine administration; by the 10th day there was almost complete tolerance to the challenging dose. Dose-response curves of acetylcholine, 5HT or histamine of 10 day control (unchallenged) tissue showed essentially no change compared with uninjected animals. The potency of exogenous morphine in blocking electrical stimulation was also unchanged and thus tolerance to injected morphine cannot be explained by reduced sensitivity of the drug for the opiate receptor. However, tissues of chronically morphinized animals gave a contraction with naloxone, extent of contraction increasing with time of drug administration. This naloxone effect has been attributed to displacement of morphine from an induced new opiate receptor (Ehrenpreis et al, op cit) which may be involved in tolerance to injected drug.

EIDELBERG, E. and BARSTOW, C.A. Effects of morphine on hypothalamic electrical activity in monkeys. Committee on the Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council, 1971.

Morphine administration in monkeys produced paroxysmal "epileptic" or "epileptord" discharges at the time in which the animals appeared to be sedated by the narcotic. This phenomenon was temporarily blocked by concurrent administration of an opioid antagonist. Both tolerance and disappearance of tolerance after withdrawal were also observed. No discharges of this type were observed during precipitated abstinence.

EIDELBERG, E. and BARSTOW, C.A. Morphine tolerance and dependence induced by intraventricular injection. Science 174: 74-76 (1971)

Injection of small quantities of morphine into the cerebral ventricular system of awake, relatively unrestrained, monkeys depressed or abolished operant food-reinforced lever pressing. After repreated Injections progressively higher doses of morphine were needed to depress responding. Also, dependence could be demonstrated in these animals by precipitating specific abstinence signs with an antagonist.

EIDELBERG, E. and BOND, M.L. Effects of morphine and antagonists on hypothalamic cell activity. Archives internationales de Pharmacodynamie et de Therapie 196: 16-24 (1972)

These experiments were carried out on urethane-anesthetized rats. The activity of single cells in the anterior hypothalamic region was recorded extracellularly, and the effects of low doses of morphine, given intravenously, were assessed on the firin frequency and pattern of these units. Both "naive" and morphine-dependent rats were used. In addition, precipitated abstinence was induced in dependent rats by an antagonist (Naloxone). Both morphinization and precipitated abstinence resulted in marked changes the frequency and pattern of discharge of the great majority of cells studied. In the naive animals morphine depressed firing and naloxone did not modify it substantially. In dependent rats low doses of morphine produced marked acceleration of cell firing, and so did naloxone. However, morphine caused a bursting type of discharge while naloxone did not. We conclude that the hypothalamus is an important locus of action of opioid narcotics, and that it may become possible to interpret their cellular mechanisms of action in terms of present knowledge of synaptic transmitter action.

EIDELBERG, E. and ERSPAMER, R. Dopaminergic mechanisms of opiate actions in brain. The Journal of Pharmacology and Experimental Therapeutics (in press)

EIDELBERG, E. and ERSPAMER, R. Failure of naloxone to prevent acute morphine tolerance and dependence. Archives internationales de Pharmacodynamie et de Therapie 211(1): 58-63 (1974)

Concurrent administration of an opioid antagonist with morphine antagonized analgesia, but not acute tolerance and dependence in mice.

EIDELBERG, E., ERSPAMER, E., KREINICK, C. and HANIS, J. Genetically determined differences in the effects of morphine on mice. European Journal of Pharmacology (in press)

EIDELBERG, E. and LOSHIAVO, C.M. Effects of morphine and opioid antagonists on the central nervous system. Committee on the Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council, 1969.

EIDELBERG, E. and SCHWARTZ, A.S. Possible mechanisms of action of morphine on brain. Nature 225(5238): 1152-1153 (March, 1970)

ELLINWOOD, E.H., JR. Chronic amphetamine intoxication in several experimental animals. Psychopharmakologie 4:351 (1971)

ELLINWOOD, E.H. JR,, SUDILVOSKY, A. and GRABOWY, R. Olfactory forebrain seizures induced by methamphetamine and disulfiram. Biological Psychiatry 7(2): 89-99 (1973)

A combination of disulfiram and methamphetamine was administered to cats over a period of days in doses sufficient to induce generalized seizures. The original anatomical focus of discharge and process of seizure development were studied. High-voltage olfactory bulb spindle activity appeared to induce epileptic discharges which emanated from the anterior olfactory system (olfactory bulb and tubercle, accumbens, and amygdala). Computer analysis showed that the spindle activity which preceded the discharges formed a recognizable pattern with the discharges. The substantia nigra and interpeduncular nucleus were involved in the spread of seizure discharges leading to generalized seizures. Norepinephrine was implicated as an inhibitor of seizure activity; dopamine may potentiate seizure activity. The importance of electrographic events in relation to the mechanisms underlying psychomotor epilepsy and amphetamine psychosis is stressed.

ELLIOTT, H.W. and CUMMINS, J.T. Effect of morphine on the K + induced increase in the level of NAD (P)H in brain slices. Federation Proceedings (in press)

The level of NAD(P)H in brain cortex slices from control and morphine-tolerant (implanted pellet) rats was measured by dual wavelength spectrophotometry. The steady state level of NAD(P)H in slices from both groups of rats was increased by the addition of 30 mM K+ to low Ca++ (0.19 mM) and to normal Ca++ (0.75 mM) containing media. The K+ induced response in slices respiring in low Ca++ but not in normal Ca++ containing media and obtained from control but not from morphine-tolerant rats was inhibited by 2×10^{-3} M morphine. Cortex slices made from morphine-tolerant rats given 10 mg/kg naloxone i.p. one hour earlier gave the same response to K+ as slices from control or morphine-tolerant rats and the same response to morphine as slices from control rats. Similar results were obtained with slices from the caudate nucleus. The results indicate that the effects of morphine on brain slice metabolism involve Ca++ and that the site (or receptor) at which morphine acts is modified in the tolerant rats in some manner that involves Ca++.

FAITH, M.E., YOUNG, L.D., GRABARITS, F. and HARVEY, J.A. Differences in the duration of reserpine action in the rat depending on the measure employed. International Journal of Neuropharmacology 7:575-585 (1968)

The effects of reserpine were determined on eleven measures of drug action at 2, 26, and 50 hr following an acute injection. All measures were almost equally affected at 2 hr after injection and estimates of ED-50 from the log dose-effect curves ranged from 1.20 to 2.12 mg/kg. There were large differences, however, between the various indices in the time required for recovery from reserpine action. Five separate patterns of recovery could be distinguished. (1) Complete recovery within 26 hr; tremor and conditioned escape. (2) Partial recovery at 26 hr and complete recovery by 50 hr; muscle tone and hunched posture. (3) Little or no recovery at 26 hr but complete recovery by 50 hr; ptosis, exploratory behavior and lever pressing on variable interval schedules. (4) No recovery at 26 hr and only partial recovery by 50 hr; spontaneous locomotor activity and lever pressing on a continuous reinforcement schedule. (5) No recovery at 26 or 50 hr; the conditioned avoidance response. These differences in the duration of reserpine action are discussed with respect to differences in duration of neurochsmical effects of the drug on monoamine in the brain.

FANN, W.E., DAVIS, J.M., JANOWSKY, D.S. and OATES, J.A. Amine uptake in the pharmacology of affective disorders. Biogenic Amines in Psychiatry. Edited by S. Gershon and W. Bunney. New York: Plenum Publlshing Company, 1973.

FANN, W.E., DAVIS, J.M., JANOWSKY, D.S., KAUFMANN, J.S., GRIFFITH, J.D. and OATES, J. A. Effect of iprindole on amine uptake in man. Archives of General Psychiatry 26(2): 158-162 (February, 1972)

Iprindole is a clinically effective antidepressant similar to other tricyclic drugs in structure. In animal studies it does not appera to inhibit the levarterenol membrane pump. Investigation was made of iprindole's effect on the peripheral adrenergic levarterenol pump in man utilizing blood pressure response to tyramine and Levarterenol. Other clinically effective tricyclic drugs exert, by blocking its uptake, a potent blocking effect on the blood pressure response to tyramine and, in a similar manner, augment the pressure response to infused levarterenol. In contrast, iprindole showed no significant effect on tyramine and levarterenol blood pressure response. Other tricyclics also reduce-platelet serotonin content, probably by inhibiting membrane uptake of this amine. Iprindole failed to alter platelet serotonin content. These findings call into quedtion that aspect of the biogenic amine theory of depression which states that the tricyclic drugs exert their antidepressant action by inhibiting the membrane pump. The clinical implications for cardiovascular toxicity is discussed.

FEINBERG, I. Absence of REM rebound after barbiturate withdrawal. Science 185: 534-535 (August, 1974)

Administration of three different barbiturates reduced rapid eye movement (REM) sleep. Drug withdrawal led to a return to baseline REM values without significant overshoot. Similar results are observed with administration of benzodiazepin: in pharmacologically equivalent dosages; therefore, a distinction between these two drug classes on the basis of withdrawal effects on the sleep electroencephalogram appears unwarranted. Further investigation is required to determine why high REM levels are sometimes associated with the withdrawal of sedative-hypnotic agents.

FEINBERG, I., HIBI, S., BRAUN, M., CAVNESS, C., WESTERMAN, G. and SMALL, A. Sleep amphetamine effects in MBDS and normal subjects. Archives of General Psychiatry 31: 723-731 (November, 1974)

Electroencephalographic sleep patterns in children with minimal brain dysfunction syndrome (MBDS or hyperkinesis) before and during stimulant treatment differed little from those of age-matched controls. It is unlikely that the therapeutic mechanisms of amphetamines in MBDS are exerted on or reflected in physiological sleep patterns.

Neither MBDS children nor normal young adults showed withdrawal elevations of rapid eye movement (REM) sleep after administration of amphetamines in constant dosage. Young adults showed REM rebounds only when the dosage was increased prior to withdrawal.

In contrast to sedative-hypnotics, stimulant drugs do not reduce eye movement activity during REM sleep. This difference is emphasized for the specificity hypothesis--that different classes of psychoactive drugs differentially alter physiological sleep patterns--would be untenable if sedatives and stimulants produced the same effects on sleep.

FEINBERG, M.P. and COCHIN, J. Effect of weekly doses of cyclohexamide on tolerance to morphine in the rat. The Pharmacologist 11: 256 (1969)

In continuing previously reported work (Feinberg and Cochin, The Pharmacologist: 10: 188, 1968) we decided to test the effect of cycloheximide (CX) on the development of tolerance to morphine sulfate (MS) in the rat. Although Way, et. al. have shown that chronic CX inhibits the development of tolerance and physical dependence in the mouse (Science, 162: 1290, 1968), we chose CX because it inhibits protein synthesis appreciably when given acutely, while cyclophosphamide does so only on chronic administration. Male rats were divided randomly by weight into two groups: A (CX + MS) and B (MS). All rats received MS (10 mg/kg. s.c.) weekly, and were tested every other week for analgesic response by the hot-plate method of Eddy and Leimbach. Rats in Group A received CX (1 mg/kg, s.c.) one hour before each weekly injection of MS. On test days, CX was given immediately after the baseline readings were obtained.

FEINBERG, M.P. and COCHIN, J. Effects of cyclophosphamide (cytoxen) on tolerance to morphine. The Pharmacologist 10: 188 (1968)

Cochin and Kornetsky (J. Pharmacol 145: 1, 1964) have hypothesized that tolerance to narcotic analgesics may be an immune phenomenon. We wished therefore, to test the effect on tolerance of a drug which inhibits protein synthesis and affects the immune response. Male rats (Goffmoor Farms) were randomized by weight into two groups: A (treated) and B (control). Group A received 10 doses of cyclophosphamide (CP), each 15 mg/kg, spread evenly over 3 weeks. On the day of the 10th injection (day 22) all rats received 10 mg/kg of morphine sulfate (MS). Analgesic response was tested by the hot-plate method of Eddy and Leimbach (J. Pharmacol. 107: 385, 1953) All rats again received MS on days 29 and 36, and were tested for analgesia as above. Rats in group A received CP, 15 mg/kg, on days 28 and 35. Rats in group B never received CP. Rats in group A showed significantly less tolerance to MS than did rats in group B. Data were analyzed by analysis of covariance performed on an IBM 360 computer.

FINK, M. Brain, behavior and anticholinergic drugs. Anticholinergic Drugs and Brain Functions in Animals and Man. Edited by P. Bradley and M. Fink. Amsterdam, the Netherlands: Elsevier, 1967. Pp. xii-xvi.

FINK, M. Drugs, EEG, and behaviour: EEG profiles and bioavailability measures for clinical psychopharmacology. Electroencephalography and Clinical Neurophysiology 34: 754 (1973).

FINK, M. EEG classification of psychoactive compounds in man: Review and theorv of behavioral associations. Psychopharmacology: A Review of Progress, 1957-1967. Edited by D. Efron, J. Cole, J. Levine and J.R. Wittenborn. Washington, D.C.: U.S. Government Printing Office, 1968. Pp. 497-507.

For abstract, see Section I. Methodology of Drug Research.

FINK, M. EEG effects of drug dependence. Clinical and Biological Aspects of Drug Dependence. Edited by S.J. Mule and H. Brill. Cleveland, Ohio: Chemical Rubber Company Press, 1972.

FINK, M. Effects of cannabis on human EEG and heart rate--evidence of tolerance development on chronic use. Psychopharmacology, Sexual Disorders and Drug Abuse. Edited by T.A. Ban, J.R. Boissier, G.J. Gessa, H. Heimann, L. Hollister, H.E. Lehmann, I Munkvad, H. Steinberg, F. Sulser, A. Sundwall and O. Vinar, Amsterdam, the Netherlands: North-Holland Publishing Company, 1973.

FINK, M. EEG and human psychopharmacology. Annual Review of Pharmacology 9: 241-258 (1969)

Psychoactive drugs affect behavior through biochemical alterations of the central nervous system. The methods of measuring changes in CNS activity in man are limited to measures applicable to the intact organism so that most studies have been focused on the scalp-recorded EEG.

Problems of dosage, route and duration of drug administration, location of electrodes and qualities of amplifiers, state of vigilance of the subject, 'and the methods of neurophysiological analysis provide great variations in the data. Changes in frequency, power, and amplitude of the waking and the sleep EEG are the principal parameters studied. The averaged evoked response to sensory stimulation is also frequently studied.

Despite variations in methods and populations, psychoactive drugs induce characteristic changes in the human scalp EEG which bear direct relations to the associated behavioral changes. Reports of "dissociation" of EEG 'and behavior with anticholinergic drugs are special instances 'of insufficient definitions of behavior and EEG in animals, and when these drugs are studied in man with better definitions of the relevant variables, dissociation is 'not evident.

The EEG-psychoactive literature is consistent with a theory of association of EEG and behavior. Applications are described in the classification of psychoactive drugs by EEG criteria, in the identification of compounds for clinical trial, in providing biological models of classifications of mentally ill populations, and in studies of the pathophysiology of disordered mental states.

FINK, M. Levomethadyl (LAAM): A long-acting substitute for methadone in maintenance therapy of opiate dependence. Current Psychiatric Therapies. Edited by J.H. Masserman. New York: Grune and Stratton, 1973.

FINK, M. Marihuana, EEG and behavior. Annals of the New York Academy of Science 191: 206-215 (1971)

FINK, M. Neurophysiology of the phantastica: EEG and behavioral relations in man. Psychopharmacology: A Review of Progress, 1957-1967. Edited by D. Efron, J. Cole, J. Levine and J.R. Wittenborn. Washington, D.C.: U.S. Government Printing Office, 1968.

A review of the changes in the spontaneous EEG of alert man in response to a wide variety of hallucinogens indicates that characteristic associations of EEG and behavior occur.

Decreased EEG alpha abundance and increased fast frequencies are characteristic of active hallucinogens. The altered consciousness associated with some hallucinogens (deliriants, thymoleptic drugs) is accompanied, in addition, by an increase in the abundance of EEG slow wave activity.

These patterns are part of a theory of the association of changes in the alert EEG and human interactive behavior in response to psychoactive drugs.

FINK, M. Psychoactive drugs, brain function and human behavior. Proceedings of the World Congress on Psychiatry. Amsterdam, the Netherlands: Excerpta Medica Foundation, 1974.

FINK, M. Questions in cyclazocine therapy of opiate dependence. Opiate Addiction: Origins and Treatment. Edited by S. Fisher and A. Freedman. Washington, D.C.: V.H. Winston and Sons, Inc., 1974.

FINK, M. A rational therapy of opiate dependence: Narcotic antagonists. Drug Abuse: Proceedings of the International Conference. Edited by C. J. D. Zarafonetis. Philadelphia, Pennsylvania: Lea and Febiger. 1971.

FINK, M. Treatment and prevention of opiate dependence. Contemporary Drug Problems Washington, D.C.: Federal Legal Publications, 1972.

FINK, M. and BRADLEY, P. Anticholinergic drugs and brain function in animals and man. Neuropsychopharmacolopy. Edited by H. Brill. Amsterdam, the Netherlands: Excerpta Medica Foundation, 1967.

The symposium reviewed recent studies of the neurophysiological and behavioral effects of anticholinergic agents in animals and man focusing on the role of cholinergic mechanisms in behavior, the question of dissociation of EEG and behavior, and new techniques for evaluation of cholinergic mechanisms.

FINK, M. and ITIL, T. Anticholinergic hallucinogens and their interactions with centrally active drugs. Neuropsychopharmacology. Edited by H. Brill. Amsterdam, the Netherlands: Excerpta Medica Foundation, 1967.

In a study of the effects of Ditran and of atropine, three patterns of behavioral and EEG effects were described, and related to differences in dosage.

FINK, M. and ITIL, T. EEG and behavioral aspects of the interaction of anticholinergic hallucinogens with centrally active compounds. Anticholinergic Drugs and Brain Functions in Animals and Man. Edited by P. Bradley and M. Fink. Amsterdam, the Netherlands: Elsevier, 1967. Pp. 149-166.

FINK, M. and ITIL, T.M. EEG and human psychopharmacology. IV: Clinical antidepressants. Psychopharmacology: A Review of Progress, 1957-1967. Edited by D. Efron, J. Cole, J. Levine and J.R. Wittenborn. Washington, D.C.: U.S. Government Printing Office, 1968. Pp. 671-682.

For abstract, see Section I. Methodology of Drug Research.

FINK, M., ITIL, T.. ZAKS, A. and FREEDMAN, A. EEG patterns of cyclazocine. a narcotic antagonist. Neurophysiological and Behavioral Aspects of Psychotropic Drugs. Edited by A. Kareczman and W.P. Koella. Philadelphia, Pensylvania: C.C. Thomas, 1971.

As part of a clinical evaluation of cyclazbcine, EEG studies were undertaken to determine the relation, if any, between the induced EEG patterns, the clinical efficacy and the psychoactive classification of cyclazocine. The studies also served as a measure of the degree of antagonism between cyclazocine and the acute administration of opiates.

FINK, M. and SHAPIRO, D. M. EEG indices of CNS bioavailability of psychoactive drugs. Electroencephalography and Clinical Neurophyeiology 33: 246-247 (1972)

For abstract, see Section I. Methodology of Drug Research.

FINK, M. and SHAPIRO, D.M. EEG patterns as an index of clinical activity of psychoactive drugs. Electroencephalography and Clinical Neurophyeiology 27: 710 (1969)

For abstract, see Section I. Methodology of Drug Research.

FINK, M., SHAPIRO, D.M. and ITIL, T.M. EEG profiles of fenfluramine, amobarbital and dextroamphetamine in normal volunteers. Psychopharmacologia 22: 369-383 (1971)

A quantitative EEG study in volunteer adults was undertaken to distinguish single oral administrations of 50 and 100 mg amobarbital, 10 mg dextro-amphetamine, 40 mg fenfluramine and placebo. Four hour EEG recordings were monitored by frequent auditory reaction time tasks. The EEG changes were measured by digital computer period analysis.

In the analysis, each drug was distinguished from placebo, and from each other, with the best discriminations for 50 mg amobarbital and dextroamphetamine, and the poorest discrimination of fenfluramine from 50 mg amobartbital.

These observations are consistent with the clinical pharmacology of the compounds and suggest further applications of quantitative EEG for the classification of psychoactive drugs.

FINK, M., SIMEON, J., ITIL, T. and FREEDMAN, A. Clinical antidepressant activity of cyclazocine - a narcotic antagonist. Clinical Pharmacology and Therapeutics 11(1): 41-48 (1970)

Cyclazocine is a benzomorphan derivative with analgesic and antinarcotic activity. During a clinical evaluation in the treatment of opiate dependence, elation, insomnia and increased libido with administration and a "grippe-like" syndrome on acute withdrawal were recorded as secondary effects. In the scalp-recorded electroencephalogram (EEG), desynchronization, decreased alpha abundance, and increased fast and theta activities were recorded concurrently. Because the clinical and EEG patterns were most similar to those with the tricyclic antidepressants, a clinical trial in depressive disorders was undertaken. In an open clinical trial in severely depressed chronic mentally ill patients, improvement in depressive symptoms and in clinical evaluations occurred within 4 weeks in 8 of 10 subjects, receiving 1.0 to 3.0 mg of cyclazocine daily. In a clinical trial in imipramine treatment failures in an outpatient mental health clinic, 10 of 19 patients improved in depressive symptoms within 8 weeks as dosages of 1.0 to 3.0 mg. daily. In both studies, secondary effects were common, suggesting a narrow therapeutic range. Cyclazocine is an active antidepressant as well as an active antinarcotic agent. The antidepressant activity is correlated with the EEG patterns and is consistent with recent EEG classifications of psychoactive drugs. The antidepressant activity does not seem to be related to the antinarcotic activity. In the treatment of opiate dependence, the efficacy of cyclazocine may be related in part to its antidepressant activity.

FINK, M., VOLAVKA, J., DORNBUSH, R. and CROWN, P. Effects of THC-delta-9, marijuana and hashish on EEG, mood and heart rate in volunteers. Psychopharmacologia 26: 126 (1972)

Male volunteers received varying doses of cannabis by smoking marijuana, hashish, THC-delta-9 impregnated oregano, and, as placebo, either oregano or THC-free marijuana in consecutive studies. Dosages equivalent to 8 to 25 mg THC-delta-9 were smoked in 4-8 minutes.

EEG changes were of rapid onset (within the smoking period) and included increased alpha abundance, decreased beta and theta activities. EEG changes were accompanied by subjective feelings of euphoria and by tachycardia. These effects were dose-related.

In chronic administration of 14 mg THC-delta-9 daily for 21 days, volunteers exhibited similar effects on EEG, heart rate, and behavior. The changes decreased on successive exposures, suggestive of "tolerance". No adverse effects were observed.

FINK, M., ZAKS, A., RESNICK, R.B. and FREEDMAN, A. M. Narcotic antagonists in the treatment of opiate dependence. International Journal of Clinical Pharmacology, Therapy and Toxicology 4: 455-458 (1971)

In our trials with a pharmacologic-rehabilitation approach to the treatment of opiate dependence, my associates and I confirmed the reports of the therapeutic efficacy of methadone; we are concerned with the too rapid acceptance of this model for political expedience; we are satisfied with the initial clinical efficacy of antagonists, particularly cyclazocine; and we are hopeful that the development of a long-acting naloxone will provide a specially useful therapy of opiate dependence.

FINK, M., ZAKS, A., RESNICK, R. and FREEDMAN, A.M. Opiate antagonists in the treatment of heroin dependence in man. Narcotic Drugs: Biochemical Pharmacology. Edited by D. Clouet. New York: Plenum Press, 1971.

This report describes our clinical trials with cyclazocine and naloxone in an effort to provide "engagement" to the rehabilitation program and to test the conditioning theory or opiate dependence.

In these studies of antagonists, randomly assigned subjects have also received other agents, such as methadone (Freedman at. al., 1967; Resnick et. al., in press: Zaks et. al., 1969: Roubicek et. al., in preparation) and tybamate (Veress et. al., 1969). The subjects of these studies are male opiate addicts who volunteered for admission to an in-patient treatment center in a municipal hospital in the East Harlem section of New York City. The population of this community is very low income, predominantly Negro and 'Puerto Rican, with low educational levels and large numbers receiving extensive welfare assistance. The ages for those reported here ranged from 17 to 54 with a mean of 26 years, and the duration of addiction was 2 to 30 years. All patients applying for treatment were accepted for cyclazocinc induction except those who were actively psychotic, dependent on non-narcotic drugs or physically ill.

Male patients applying for treatment are asked to sign a permit for an '"experimental" treatment of their addiction. Some volunteered and were placed on a waiting list but never appeared for admission. Others left during the detoxification period or immediately thereafter.

On admission to the study ward, the narcotic usage of each patient is estimated by inquiry. Methadone is given in reducing amounts for detoxification, usually within four to seven days, and a drug-free period of observation allows medical and laboratory examinations before induction with an antagonist.

FINK, M., ZAKS, A., VOLAVKA, J. and ROUBICEK, J. Electrophysiological studies of opiates and antagonists in man. Narcotic Drugs: Biochemical Pharmacology. Edited by D. Clouet. New York: Plenum Press, 1971.

FISHMAN, J., NORTON, B. and HAHN, E. Differential distribution of opiate agonists and antagonists in the rat brain as determined by double isotope techniques. Presented at Meeting of the American Society of Biological Chemists, 1974.

For abstract, see Section I. Methodology of Drug Research.

FITZWATER, J.E., WHITE, R.P. and NASH, C.R. Selective blockade by mephentermine of reserpine -induced scrotonin depletion. Experientia 24: 698 (1968)

FOG, R. On stereotypy and catalepsy: Studies on the effect of amphetamines and neuroleptics in rats. Acta Neurologica Scandinavia 48(Supplement 501 (1972)

FOG, R. and PAKKENBERG, H. Loss of brain cells in rats after long-term neuroleptic treatment. Presented at the First World Congress of Biological Psychiatry, Buenos Aires, Argentina, September, 1974.

FOG, R.L., Role of the corpus striatum in typical behavioral effects in rats produced by both amphetamine and neuroleptic drugs. Acta Pharmacologia et Toxicologia 24(Supplement 4): 59 (1967)

FOG, R.L. and PAKKENBERG, H. Behavioral effects of dopamine and p-hydroxy-amphetamine injected into corpus stilatum of rats. Experimental Neurology 31: 75-85 (1971)

Bilateral intrastriatal 5-mu-1 microinjections of p-hydroxyamphetamine (100 mu-g/side) and of dopamine (200 mu-g/side) were made in awake rats. Neither drug passes the blood-brain barrier well. The injections gave rise to a stereotyped hyperactive behavior similar to that seen after subcutaneous injection of amphetamine. Control injections in the thalamus and hippocampus were without effect, neither were injections of noradrenaline (100-200 mu-g side) in the corpus striatum. Spreading of tritiated dopamine intracerebrally was controlled by using autoradiography and scintillation counting. These experiments, along with earlier ones, strongly indicate that the amphetamine-type of stereotyped behavior is mediated through dopaminergic mechanisms in the corpus striatum.

FOG, R.L. and PAKKENBERG, H. Intracerebral lesions causing stereotyped behaviour in rats. Acta Neurologica Scandinavia 47: 475-484 (1971)

Bilateral lesions performed with a microcannula in corpus striatum, hippocampus or thalamus induce in reserpinized rats a stereotyped hyperactive behaviour for 6-8 min consisting of continuous biting without normal activities and resembling the amphetamine induced stereotypy. Bilateral cannula lesions of the dorsal cortex give a shorter response. The behavioural response is not influenced by inhibition of dopaminergic mechanisms in the brain and is prolonged by pretreatment with an anti-cholinergic drug. This lesion stereotypy is thus of neither dopaminergic nor cholinergic origin and, therefore, differs from the amphetamine stereo-typy (dopaminergic) as well as the paradoxical reserpine stereotypy (cholinergic). Pretreatment with DOPA or a small dose of amphetamine as well as intracerebral injection of 25% KCl or saline does not change the stereotypy.

FOG, R.L., RANDRUP, A. and PAKKENBERG, H. Chlorpromazine and related neuroleptic drugs in relation to the corpus striatum in rats. The Present Status of Psychotropic Drugs. Edited by A. Cerletti and F. Bove. Amsterdam, the Netherlands: Excerpta Medica Foundation, 1969. Pp. 278-279.

FOG, R.L., RANDRUP, A. and PAKKENBERG. H. lntrastriatal injection of quaternary butyrophenones and oxypertine: Neuroleptic effects in rats. Psychopharmacologia 19: 224-230 (1971)

Bilateral intrastriatal microinjections in rat brains of quaternary neuro-leptic drugs of the butyrophenone type (haloperidol, benperidol, floropipamide) and the indole type (oxypertine) antagonize amphetamine-induced stereotyped behaviour, with the development of catalepsy. These two behavioural effects are also typical for neuroleptics given subcutaneously. No effect was observed when placebo was injected intrastriatally or when quaternary haloperidol was injected into the thalamus or hippocampus. The neuroleptic effect may be exerted through dopaminergic mechanisms in the corpus striatum.

FOG, R.L., RANDRUP. A. and PAKKENBERG, H. Lesions in corpus striatum and cortex of rat brains and the effects of pharmacologically induced stereotyped, aggressive and cataleptic behaviour. Psychopharmacologia 18: 346-356 (1970)

Large bilateral lesions affecting 30-90% of the corpus striatum inhibit stereotyped behaviour in rats injected subcutaneously with amphetamine, but do not prevent rage reactions induced by injection of a monoamine oxidase inhibitor followed by injection of 1-dopa. The stereotyped phase normally following this rage reaction is, however, absent in the operated rats. Small bilateral lesions in the corpus striatum (5-20%) cause a modified amphetamine stereotypy and prevent the usual cataleptic behaviour produced by subcutaneous injection of a neuroleptic drug (perphenazine). Additional ablation of. the overlying dorsal cortex enhances these behavioural effects without qualitative changes. Both amphetamine and neuroleptics seem thus to mediate their behavioural effects through dopaminergic mechanisms in the corpus striatum.

FOG, R.L., RANDRUP, A. and PAKKENBERG, H. Neuroleptic action of quaternary chlorpromazine and related drugs injected into various brain areas in rats. Psychopharmacologia 12: 428-432 (1968)

In rats micro-injections in corpus striatum of quaternary chlorpromazine and related drugs give rise to highly characteristic neuroleptic effects; antagonism of amphetamine-induced stereotyped behaviour and development of catalepsy. There is no effect of injections in hippocampus or septum. Dopaminergic mechanisms in corpus striatum seem to play a central role in neuroleptic action.

FOOTE, W.E., SHEARD, M.H. and AGHALANIAN, G.K. Comparison of effects of LSD and amphetamine on midbrain raphe units. Nature 222(5193): 567-569 (1969)

To determine whether the inhibition of raphe neurons is specific for LSD and related psychotogenic compounds or whether this effect would generally follow from any sort of stimulant, an investigation has been made comparing the effects of LSD and amphetamine. The study showed that amphetamine failed to inhibit raphe units and hence the inhibitory effect of LSD on these units cannot be explained in terms of some non-specific stimulant action.

FORBES, J.E., DEWEY, W.L. and HARRIS, L.S. The effect of narcotics and narcotic antagonists on ganglionic transmission in rat. Federation Proceedings (in press)

For abstract, see Section II. Drug Chemistry and Metabolism.

FORD, D.H., RHINES, R.K. and VOELLER, K. Morphine effects on neurons of the median eminence and on other neurons. Narcotics and the Hypothalamus. Edited by E. Zimmermannand R. George. New York: Raven Press, 1974.

FORD, D.H., VOELLER, K., CALLEGARI, B. and GRESIK, E. Changes in neurons of the median eminence-arcuate region of rats induced by morphine treatment: A electronmicroscopic study. Neurobiology 4: 1-11 (1974)

Electronmicroscopic examination of male rats killed 2 or 24 hours after a single intraperitoneal injection of morphine sulfate (60 mg/kg) or after a 5-day series of increasing dosages given every 8 hours (starting at 30 mg/kg) demonstrated changes in the median eminence-arcuate region. This consisted of the formation of whorl bodies which appear to have been derived from the endoplasmic reticulum and which were located in the soma and dendrites of neurons. Sections from the cerebral cortex, hippocampus and the nucleus gigantocellularis showed no such change, while in one of the 5-day morphine treated animals there was a whorl body in the preoptic area. Of 5 controls, only one showed development of whorls, which were very scarce.

Synaptic vesicle changes were noted in the medianeminence-arcuate region of the morphine treated rats which represent an exaggeration and alteration in frequency of structural characteristics observed in control animals. Thus, there was an increased frequency of pleomorphism, increased packing density and increased number of synapses in which the vesicles were arranged in a crystalline-like array.

FORD, D.H., WEISFUS. D., LEVI, N. and RHINES, R.K. Accumulation of ^{3}H-1-lysine by brain and plasma in male and female rats treated acutely with morphine sulfate. Acta Neurologica 50: 53-75 (1974)

Adult male and female Wistar rats were injected with a single dose of 40 mg/kg of morphine sulfate via indwelling intrajugular cannulas and killed two hours later. ^{3}H-l-lysine was injected at various time intervals before the death of the animals. The distribution of the labelled amino acid was then determined in the free amino acid and lipid-nucleoprotein-extracted protein fractions of plasma and cerebral grey matter. The accumulation of ^{3}H-activity 'was also determined in various areas of the brain, dorsal root ganglia $_{3}$ pectoral muscle and liver. Morphine-treatment produced an elevation of free ^{3}H-activity lysine levels in plasma and cerebral grey matter and a decrease in incorporation into protein. A si nificant sex difference was noted, such that in control males the plasma free ^{3}H-lysine and protein fractions were higher than in females. In the morphine-treated group the values obtained from males were lower than for females. In cerebral grey matter, the free ^{3}H-lysine was significantly lower in control and morphine-treated males than in females. In the protein fraction, such sex differences varied with the time elapsed after injection of amino acid and did not clearly favor either sex, The accumulation of ^{3}H-activity in tissue blocks taken from various regions of CNS was unaffected by morphine-treatment in subcortical components. The values were generally higher in females. ^{3}H-accumulation was significantly altered in cortical components in the male group. In cerebral white matter, the morphine-treated males showed significant elevations of accumulation. Females showed an elevation of ^{3}H-accumulation in the morphine-treated group only when the data was subjected to a group comparison. In the peripheral nervous system, ^{3}H-accumulation was significantly depressed by morphine-treatment only in males. The female values were again significantly higher than those from the males. The male liver demonstrated a significant depression in accumulation of ^{3}H-activity in the morphine-treated group. Liver tissue from females was less responsive and had higher uptakes than in males. Skeletal muscle showed no alteration in ^{3}H-accumulation after morphine treatment in either sex.

FORREST, F.M., FORREST, I.S. and SERRA, M.T. Modification of chlorpromazine metabolism by some other drugs frequently administered to psychiatric patients. Biological Psychiatry 2:53-58 (1970)

For abstract, see Section II. Drug Chemistry and Metabolism.

FORREST, I.S. The nature of the interaction between melanin and drugs. Psychopharmacology Bulletin 10(4): 38-40 (1974)

FORREST, I.S., FORREST, F.M. and SERRA, M.T. Chlorpromazine retention. American Journal of Psychiatry 126: 271-272 (August, 1969)

FREEMAN. J.J. and SULSER, F. Iprindole-amphetamine interactions: The role of aromatic hydroxylation of amphetamine in its mode of action. The Journal of Pharmacology and Experimental Therapeutics 183:307-315 (1972)

The present investigations were undertaken to study the mechanism by which iprindole enhances the psychomotor stimulation (locomotor and stereotyped activity) of amphetamine and to elucidate the role of the hydroxylated metabolites of amphetamine in its mode of action. The enhanced psychomotor stimulation and the increased levels of amphetamine in tissue after iprindole pretreatment resulted from an inhibition of the p-hyroxylation of amphetamine. Iprindole markedly reduced the accumulation of p-hydroxyamphetamine in urine and p-hydroxymorephedrine in tissue after the administration of amphetamine. Since pretreatment with iprindole enhanced' the central action of amphetamine and did not prevent the initial depletion of norepinephrine in brain or heart, the formation of the hydroxylated metabolites of amphetamine does not seem to be required for these pharmacological or biochemical effects. The maintenance of depletion of norepinephrine caused by amphetamine, however, was associated with the accumulation of p-hydroxynorephedrine in tissue. Unlike desipramine, iprindole altered neither the initial accumulation nor the metabolism of tritiated norepinephrine in brain or heart. The results show that iprindole is a "cleaner" tool to study the mechanism of action of amphetamine and suggest that a blockade of the neuronal membrane pump is not a requirement for the therapeutic efficacy of tricyclic antidepressants.

FREEMAN, J.J. and SULSER, F. On the peripheral mode of action of amphetamine and desipramine. Presented at the Fifth International Congress on Pharmacology, San Francisco, California, 1972.

FREY, L.G. and WINTER, J.C. Effects of p-acetyldeoxyephedrine on punished behavior in the rat. Archives internationales de Pharmacodynamie et de Therapie 201(1): 125-127 (1973)

Rats were trained to press a bar for food on a multiple schedule in which one component was VI 30 (food) and the other was FR 10 (concurrent food and, electric shock). The effects of p-acetyldeoxyephedrine (p-ADE), a drug which produces a transient decrease in tissue levels of 5-hydroxytryptamine (5-HT), were then examined. It was found that the doses of p-ADE which are required to deplete 5-HT produce nonspecific suppression of operant behavior. These observations suggest that p-ADE is not suitable for the study of the effects of 5-HT depletion on operant behavior in the rat.

FRIEDEL, R.O., BERRY, D.E. and SCHANBERG. S.M. Effects of dopamine and norepinephrine on phospholipid metabolism of rat brain in vivo: Regional differences. Journal of Neurochemistry 22: 873 (1974)

FRIEDEL. R.O., JOHNSON, J.R. and SCHANBERG, S.M. Effects of sympathomimetic drugs on incorporation in vivo of intracisternally injected ^{33}Pi into phospholipids of rat brain. The Journal of Pharmacology and Experimental Therapeutics 184(3): 583 (1973)

The effects of norepinephrine, phenylephrine, isoproterenol, henoxybenzamine and carbamylcholine on the incorporation in vivo of Pi into phospholipids of rat brain were studied at 5 and 30 minutes after intracisternal injection of the radionuclide. Norepinephrine, an alpha and beta adrenergic stimulator, and phenylephrine, an alpha adrenergic stimulator, enhanced the labeling of phosphatidic acid and phosphatidyl inositol at both times, whereas isoproterenol, a beta adrenergic stimulator, had no effect. Phenoxybenzamine, an alpha adrenergic blocking agent, blocked the stimulatory effect of norepinephrine and phenylephrine. The pattern of stimulation of individual phospholipids by norepinephrine was different from that of carbamylcholine, a cholinomimetic agent, in that norepinephrine had a significantly greater effect on the labeling of phosphatidic acid and had no effect on the labeling of phosphatidyl choline, a phospholipid markedly stimulated by carbamylcholine. These studies suggest that the metabolism of phosphatidic acid and phosphatidyl inositol in rat brain is associated with rapid membrane process controlled in part by alpha adrenergic mechanisms and differ from the effects on phospholipid metabolism which are produced by cholinergic mechanisms. The data also indicate that the metabolism of phosphatidyl choline may be related to slower membrane processes controlled by cholinergic mechanisms.

GAONI, Y. and MECHOULAM, R. Hashish XIV. The iso-tetrahydrocannabinols. Israeli Journal of Chemistry 6:679 (1968)

For abstract, see Section II. Drug Chemistry and Metabolism.

GARRETT, E.R., BRES, J., SCHNELLE, K. and ROLF, L.L., Jr. Pharmacokinetics of saturably metabolized amobarbital. Journal of Pharmacokinetics and Biopharmaceutics 2(1): 43-103 (1974)

For abstract, see Section I. Methodology of Drug Research,

GEBHART, G.F. and MITCHELL, C.L. Strain differences in the response to morphine as measured on the hot plate. Archives internationales de Pharmacodynamie et de Therapie 201: 128-140 (1973)

The relationship of brain monoamines, especially 5-hydroxytryptamine (5-HT), to the analgesic effect of morphine has been widely investigated. However, studies examining this relationship all suffer from the fact that monoamine synthesis-blockage or depletion of monoamines either by drug, pretreatment or lesioning is necessary to alter brain levels and consequently the experimental animal is no longer physiologically "normal" at the initiation of the study. Mice of CF1 and CFW strain obviate pre-experimental manipulation of brain monoamine levels since the brain 5-HT level as well as the 5-HT turnover rate is genetically lower in CF1 than CFW strain, whereas brain norepinephrine and dopamine levels do not differ between them (Valzelli and Garattini, 19). Using a quantitative bioassay procedure as well as quanta1 probit analysis of data obtained while determining equianalgesic morphine doses in CFW and CF1 mice, morphine was found to be 1.6 times more efficacious in CF1 strain. These results are contrary to the currently popular hypothesis that decreased 5-HT brain levels and a decreased analgesic response to morphine is related. These results notwithstanding, there was no difference between these two strains of mice in their sensitivity to a presumably painful stimulus (i.e., heat) since their pre-drug reaction times on the heated plate did not differ. Finally, there was no apparent difference in the rates of tolerance development to the analgesic effect of morphine between the two strains of mice at either of two morphine dose levels.

GELLER, I. and BLUM, K. The effects of 5-HTP on para-chlorophenylalanine (p-CPA) attenuation of "conflict" behavior. European Journal of Pharmacology 9: 319-324 (1970)

"Conflict" was induced in hungry rats by simultaneously rewarding with food and punishing with shock. lever responses made in the presence of a tone stimulus. This procedure resulted in a suppression of responses during tone stimuli. Administration of para-chlorophenylalanine (p-CPA) attenuated the conflict and reinstated the suppressed responding, an effect which persisted as long as two weeks. A 15 mg/kg dose of 5-hydroxytryptophan (5-HTP) reversed the p-CPA effects for more than 24 hr. The same dose of 5-HTP was without effect when administered to rats in which'suppressed responding had been reinstated by lowering shock levels rather than administering p-CPA. The 5-HTP reversal of p-CPA effects on "conflict" suggests, the possible interpretation that p-CPA effects are due to serotonim (5-HT) depletion.

GELLER, I., HARTMANN, R.J., CROY, D.J. and HABER, B. Attenuation of conflict behavior with cinanserin, a serotonin antagonist: Reversal of the effect with 5-hydroxytryptophan and alpha-methyltryptamine. Research Communications in Chemical Pathology and Pharmacology 7(1): 165 (January, 1974)

Cinanserin, a reported antagonist of brain serotonin, attenuated conflict behavior in rats, an action characteristic of clinically active "anti-anxiety" agents. eThe effect was counteracted by administering in conjunction with cinanserin, 5-hydroxytryptophan. the serotonin precursor known to replete brain serotonin or alpha-methyltryptamine, the long acting serotonin agonist. These findings provide additional support to the speculation that anxiolytics may derive their therapeutic efficacy through alterations in the brain serotonergic system.

GERLACH, J., NIELSEN, M. and RANDRUP, A. Effect of desipramine on rat cortex slices incubated with ^{3}H-dopamine. Psychopharmacologia 37: 341-349 (1974)

Rat cortex slices were incubated with ^{3}H-dopamine (^{3}H-DA), and the effect of desipramine (DMI) was studied on the accumulation of ^{3}H-DA and ^{3}H-noradrenaline (^{3}H-NA) in the tissue and the concentrations of ^{3}H-DA and ^{3}H-NA in the incubation medium. This effect was compared with the effect of cocaine, reserpine and FLA 63 studied by the same technique, in order to elucidate the mechanisms of action of DMI.

All the drugs induced a significant decrease of ^{3}H-NA accumulation in the cortical tissue. The ^{3}H-DA retention varied: cocaine and reserpine caused a significant decrease, FLA 63 a marked, significant increase, and DMI a slight, but significant increase. In the incubation medium, ^{3}H-DA significantly increased after DMI, cocaine and reserpine, and remained unchanged after FLA 63. In all experiments ^{3}H-NA in the medium was very low.

It is suggested that DMI in cortex slices may exert a double mechanism of action on the final step in the noradrenaline biosynthesis: 1. an inhibition of the ^{3}H-DA uptake at the level of the noradrener ic cell membrane, and 2. an inhibition of the intraneouronal transport of ^{3}H-DA to sites where it is converted to ^{3}H-NA, concomitant with an increased intraneuronal ^{3}H-DA accumulation. Other possibilities are discussed.

GERLACH. J., REISBY, N. and RANDRUP, A. Dopaminergic hypersensitivity and cholinergic hypofunction in the pathophysiology of tardive dyskinesia. Psychopharmacologia 34: 21-35 (1974)

The so-called counterbalancing dopaminergic-cholinergic system has been studied in a clinical pharmacological investigation of neuroleptic-induced tardive dyskinesia. Eight hospitalized patients between the ages of 20 and 69 years were treated with alpha-methyl-para-tyrosine (AMPT), L-Dopa, physostigimine. scopolamine and biperiden. The results were evaluated blind with the help of video-technique. AMPT (3 g daily for 3 days) significantly reduced, while L-Dopa (1200 mg daily together with a peripheral decarboxylase inhibitor for 14 days) and biperiden (18 mg daily for 14 days) significantly precipitated/aggravated the dyskinesia. The effects of physostigmine and scopolamine have varied, which is discussed in relation to the existence of both hypo- and hypercholinergic stereotype.

It is concluded that dopaminergic hypersensitivity, cholinergic hypofunction and a reduced biological buffer capacity comprise important elements in the pathophysiology of tardive dyskinesia. Simple prophylactic and therapeutic directions are given based upon this conclusion.

GESSNER, P.K. Body temperature correlates of the interaction between monoamine oxidase inhibitors and meperidine. The Pharmacology of Thermoregulation. Edited by E. Schonbaum and P. Lomax. New York: S. Karger, 1973. Pp. 473-481.

GESSNER, P.K. Induction of a diethyl ether withdrawal syndrome in mice by exposure to ether vapor. The Pharmacologist 16: 304 (1974)

The ability of alcohol and sedative-hypnotic agents to induce a characteristic withdrawal syndrome in humans and other species is well known. To determine whether this property was also common to some gaseous anesthetic agents, mice were exposed to ether vapor (25 mg/l air) for a period of 3 days. At the end of this period the 22 experimental and the 10 control (i.e. not exposed to ether) mice were individually isolated using a double blind procedure and withdrawal signs were scored at predetermined intervals using a scale developed by Goldstein (J. Pharmacol. 180, 203, 1972) for alcohol withdrawal. No withdrawal signs were observed in the control mice. Withdrawal seizures were observed in 13 of the 22 ether exposed mice. Seizure scores reached near maximum values within 30 min of withdrawal, plateaued at this level for the next 4 hrs and then decreased gradually over the next 20 hrs. in follow up experiments it was found that ether withdrawal seizures were surpressed by administration of either ethanol or phenobarbital to the withdrawn animals. These latter results raise the possibility of the existance of cross-physical dependence between ether and agents such as ethanol and phenobarbital.

GESSNER, P.K. and CLARKE, C.C. The effects of meperidine and dextromethorphan on thermoregulation in mice. Temperature Regulation and Drug Action. Edited by E. Schonbaum and J. Jacob. New York: S. Karger, 19'75.

GESSNER, P.K., CLARKE, C.C. and ADLER, M. The effect of low environmental temperature on the tranylcypromine-meperidine interaction in mice. The Journal of Pharmacology and Experimental Therapeutics 189(1): 90-96 (1974)

The effect of a low environmental temperature on the mortality resultant from the administration of tranylcypromine and meperidine 4 hours apart was investigated in mice. It was found that exposure to an environmental temperature of 2°C for 1 hour prior to meperidine administration markedly reduced mortality among animals removed from the low temperature environment after the meperidine administration and markedly increased mortality among animals continued at the low temperature, after meperidine administration. Because the tranylcypromine-meperidine interaction is normally associated with a marked hyperthermia, the body temperature correlates of the interaction were investigated in mice exposed to a low environmental temperature. Under the conditions of cold exposure, mice administered tranylcypromine and meperidine did not show a hyperthermic response but rather a hypothermic one. Further investigation showed this response to be mediated exclusively by meperidine. In related experiments intertreatment with prednisolone was found to be without effect on the mortality resultant from the tranylcypromine-meperidine interaction.

GESSNER, P.K. and GESSNER, T. The interaction of barbital and testosterone relative to their hypnotic effects. Archives internationales de Pharmacodynamie et de Therapie 201: 52-58 (1973)

Testosterone administered i.p. in corn oil to mice causes righting reflex loss the ED 50 for which is 289.6 mg/kg. Under similar conditions barbital has an ED 50 of 142.1 mg/kg. Coadministered with barbital, testosterone can act synergistically in producing righting reflex loss. At high testosterone and low barbital doses the testosterone content of ED 50 mixtures is however not significantly different from the ED 50 for testosterone. In particular the ED 50 for a 2.8:1 molar testosterone-barbital mixture is significantly greater than would be expected on the basis of simple dose additivity. This phenomenon is seen to be associated with the much shorter onset of action (29 min with an ED 50 dose) of testosterone relative to the onset of action of barbital (52 min with an ED 50 dose), whereby upon administration of a testosterone rich mixture the effects observed are almost exclusively attributable to testosterone.

GESSNER, P.K., LAROSA, R.T. and BERGSON, A. Investigation of the mechanism mediating the tremorgenic effect of LSD in mice. Federation Proceedings 28: 793 (1969)

In common with a number of other hallucinogens, LSD produces a tremor in mice which even at doses of 1 mu-mole/kg increases significantly (P less than 0.05) the muscular activity of restrained mice. To elucidate the mechanism mediating the tremorgenic effect of LSD in mice the effect of various pretreatments on the tremorgenic effect of LSD was determined. It was found that the tremorgenic effect of a 3.3 mu-mole/kg dose of LSD was enhanced by p-chlorophenylalanine (3x100mg/kg, 72, 48 and 24 hrs. prior respectively, P=0.05) and cocaine (10mg/kg, 30 min prior, P less than 0.05) and decreased by amphetamine (10mg/kg, 1 hr prior, P greater than 0.05), BOL (30 mu-moles/kg, 10 min prior, P less than 0.05), disulfiram (400 mg/kg, 12 hrs prior, P greater than 0.05), metrazole (50 mg/kg, 30 min prior, P less than 0.05) and morphine (0,5mg/kg, 20 min prior, P less than 0.05). The effect of both a 3.3 and a 10 mu-mole/kg dose of LSD was significantly (P less than 0.05) decreased by 5HTP (100mg/kg. 1 hr prior), DOPA (600 mg/kg, 15 min prior), reserpine (2 mg/kg, 4 hrs prior), and chlorpromazine (10 mg/kg, 1 hr prior). These results closely parallel those obtained when using 5-methoxy-N, N-dimethyltryptamine instead of LSD. It is tentatively concluded that the action of both these agents are mediated by their effects on brain monoamine function.

GESSNER; P.K. and SOBLE, A.G. A study of the tranylcypromine-meperdine interaction: Effects of p-chlorophenylalanine and 5-hydroxtryptophan. The Journal of Pharmacology and Experimental Therapeutics 186: 276-287 (1973)

Tranylcypromine and meperidine administered four hours apart to mice in a ratio of 3:10 by weight exhibited marked superadditivity of their toxic actions, the LD 50 of the combination being only 0.54 of that which would be expected on the basis of their individual toxicities. Pretreatment with p-chlorophenylalanine (100 mg/kg) at 72, 48 and 24 hours before the experiment markedly lowered the mortality of mice receiving tranyl-cypromine and meperidine in a 3:10 ratio four hours apart but not those receiving either tranylcypromine or meperidine alone. Intertreatment with doses of 5-hydroxytryptophan as low as 5 mg/kg one hour before meperidine administration markedly increased mortality of mice receiving the tranylcypromine-meperidine combination. Thus the toxic response of mice to the tranylcypromine-meperidine combination may be mediated by 5-hydroxytryptamine. Meperidine administration four hours after tranylcypromine resulted in a marked hyperthermic response. This response was significantly augmented if 5-hydroxytryptophan was co-administered with the meperidine. Pretreatment with p-chlorophenylalanine did not prevent the development of a hyperthermic response to meperidine in mice administered tranylcypromine four hours earlier; however, the p-chlorophenylalanine-pretreated mice had generally lower body temperatures than control mice.

GEYER, M.A. and SEGAL, D.S. Differential effects of reserpine and alpha-methyl-p-tyrosine on norepinephrine and dopamine induced behavioral activity. Psychopharmacologia 29: 131-140 (1973)

The locomotor activity of rats was monitored during the intraventricular infusion of either dopamine or norepinephrine after intrapertioneal pretreatment with saline, reserpine (5.0 mg/kg), or acute and chronic alpha-methyl-p-tyrosine (125 mg/kg - 1 or 8 days). While the hyperactivity produced by norepinephrine was potentiated 24 h after reserpine, the response to dopamine was reduced by reserpine. Chronic, but not acute, alpha-methyl-p-tyrosine enhanced the effect of norepinephrine without altering the dopamine-induced activity. These results indicate: 1. dopamine-induced hyperactivity is due to its conversion to norepinephrine, and 2. prolonged depletion of central catecholamines may result in postsynaptic receptor supersensitivity.

GEYER, M.A. and SEGAL, D.S. Shock-induced aggression: Opposite effects of intraventricularly infused dopamine and norepinephrine. Behavioral Biology 10: 99-104 (1974)

Saline, dopamine, or norepinephrine was infused into the lateral ventricles of unrestrained rats via chronically implanted cannulae. Immediately after infusion, the amount of shock-induced fighting between pairs of rats was determined. Low doses of dopamine increased the number of attacks while norepinephrine infusions markedly reduced fighting. Two weeks after intraventricular injection of 6-hydrosydopamine, when shock-induced fighting is increased, the infusion of norepinephrine, but not dopamine. reduced the amount of attack behavior. The possibility is discussed that this type of aggressive behavior is modulated in part by a balance between dopaminergic and noradrenergic systems.

GIANUTSOS, G., HYNES, M.D., PURI, S.K., DRAWBAUGH, R.B. and LAL, H. Effect of apomorphine and nigrostriatal lesions on aggression and striatal dopamine turnover during morphine withdrawal: Evidence for dopaminergic supersensitivity in protracted abstinence. Psychopharmacologia 34: 37-44 (1974)

Reliable aggression was seen in rats which were grouped 30 days after undergoing continuous withdrawal from morphine. This withdrawal aggression, associated with long-lasting effects of morphine dependence, was blocked by morphine or lesions of the nigrostriatal bundle, but not by lesions of the median forebrain bundle. When the nigrostriatal lesioned rats were treated with a small dose of aponorphine, the aggression was reinstated. Apomorphine reduced the turnover of dopamine in the 30-day withdrawn rats at doses which were ineffective in similarly housed non-dependent rats. These results suggest that animals undergoing protracted morphine abstinence show aggression due to a latent dopsminergic supersensitivity, similar to that previously reported during acute narcotic withdrawal.

GINTZLER. A.R. and MUSACCHIO, J.M. Interaction between serotonin and morphine in the guinea pig ileum. The Journal of Pharmacology and Experimental Therapeutics 189: 484-492 (1974)

Inhibition of the electrically induced contractions of the guinea-pig ileum has been shown to be a reliable index of the relative potency of various narcotic analgesics. This property suggests that this preparation might be useful in attempts to elucidate the mechanism by which morphine induces analgesia in the central nervous system. In light of the inhibitory effects of 5-hydroxytryptamine (5-HT) on the ileum and its interactions with morphine in other tissues, the effect of 5-HT on the inhibitory response of the ileum to mor hine was studied. Concentrations of 5-HT ranging from 2 X 10^{-8} to 2 X 10^{-7} M can potentiate the inhibitory effects of morphine, and vice versa; small concentrations of morphine (10^{-8}M) can potentiate the inhibitory response to 5-HT. Both of these effects can be abolished by washing. This potentiation is also observed with both nalorphine and methadone and seems to be due to a'specific interaction between 5-HT and narcotic analgesics; Similar concentrations of 5-HT have no effect on the inhibition produced by norepinephrine, and norepinephrine itself has no effect on the inhibition produced by morphine. Lysergic acid diethylamide (0.1 mu-g/ml) can antagonize the inhibitory effects of 5-HT but can also produce a marked potentiation of the response to morphine. The above suggests that 5-HT may play an essential role in the mechanism by which morphine induces analgesia in the central nervous system.

GOLDBERG, S.R. Nalorphine: Conditioning of drug effects on operant performance. Stimulus Functions of Drugs. Edited by G. Heistad, T. Thompson and R. Pickens. New York: Appleton-Century-Crofts, 1970.

GOLDSTEIN, A. Biochemistry and pharmacology of the addictive process. Abstracts of the 119th Annual Meeting of the American Pharmaceutical Association, Vol. 2. Washington, D. C.: The American Pharmaceutical Association, 1972. P. 31.

GOLDSTEIN, A. Molecular aspects of narcotic addiction. Annals of Internal Medicine 78: 813 (1973)

To understand fully the way any drug produces its pharmacologic effects, we have to learn not only where it acts (what organs, tissues, and cells are primarily affected) but also exactly what it does at the site(s) of action. Considerable progress is being made in identifying and isolating, drug receptors--the macromolecules with which drugs interact to initiate the sequence of biochemical changes that ultimately produce the characteristic drug effect in the whole organism.

The opioid narcotics are of particular interest for their ability to produce tolerance and physical dependence, which play a role in the addiction process. In this lecture I shall review recent investigations that have led to some plausible hypotheses about the sites and molecular mechanisms of narcotic action and about the molecular basis of tolerance and physical dependence.

GOLDSTEIN, A. Opiate receptor mechanism. NRP Bulletin (1974)

GOLDSTEIN, A. Opiate receptors. Life Sciences 14: 615 (1974)

GOLDSTEIN, A. Recent studies on the binding of opiate narcotics to possible receptor sites. New Concepts in Neurotransmitter Regulation. Edited by A. J. Mandell. New York: Plenum Press, 1973.

GOLDSTEIN, A. and JUDSON, B.A. Alcohol dependence and opiate dependence: Lack of relationship in mice, Science 172: 290-292 (April 16, 1971)

For abstract, see Section II. Drug Chemistry and Metabolism.

GOLDSTEIN, A., JUDSON, B.A. and SHEEHAN, P. Cellular and metabolic tolerance to an opioid narcotic in mouse brain. British Journal of Pharmacology 47(1): 138 (1973)

Running activity and brain levorphanol concentration were measured in nontolerant and tolerant mice given various doses of ^{3}H-levorphanol.

The principal factor responsible for tolerance in the mouse is a loss of sensitivity to the narcotic drug at the cellular level in brain; despite adequate brain concentrations, the pharmacological effects are dimished or absent.

There is also metabolic tolerance; a given dose establishes a lower brain concentration in tolerant than in non-tolerant animals.

The two kinds of tolerance are distinguished here and the contribution of each is assessed.

GOLDSTEIN, A., LOWERY, P.J. and LOWNEY, L.I. Increased binding of an opiate narcotic to a receptor proteolipid in the presence of naloxone. Federation Proceedings 33(3): 474 (March, 1974)

We have reported elsewhere (Science, Life Sci., in press) the partial purification of a proteolipid from mouse brain with opiate receptor (R) binding properties. Fractionation was on Sephadex LH-20 columns with increasing methanol (M) in chloroform (C); ligand-free R elutes in a 50% M fraction. After preincubation of R with the opiate agonist levorphanol (190 nM), the levorphanol-R complex elutes much earlier, in pure C. When the antagonist naloxone (100 nM) is also present in the preincubation, an additional peak of complexed levorphanol appears, and the total complexed levorphanol is increased 2- to 3-fold. At higher naloxone concentration (10-100 mu-M), Ievorphanol binding is prevented, as already reported.

It is evident from these results that naloxone and levorphanol can combine simultaneously with R. Our findings suggest the possibility that R may be an allosteric oligomer. It is not yet clear, however, in what way the phenomena observed here may relate to the phenomenon of narcotic antagonism in vivo. One interpretation is consistent with an idea advanced by one of us (A. Goldstein, First Int. Conf. on Narcotic Antagonists, in press) that agonists cause a conformation change in R, and that antagonists prevent such conformation change.

GOLDSTEIN, A., LOWNEY, L.I. and PAL, B.K. Stereospecific and nonspecific interactions of the morphine congener levorphanol in subcellular fractions of mouse brain. Proceedings of the National Academy of Sciences. 68(8): 1742-1747 (August, 1971)

For abstract, see Section I. Methodology of Drug Research.

GOLDSTEIN, A. and SHEEHAN, P. Tolerance to opioid narcotics. I. Tolerance to the "running fit" caused by levorphanol in the mouse. The Journal of Pharmacology and Experimental Therapeutics 169(2): 175-184 (1969)

The running fit induced by opioid narcotics in mice serves as a convenient graded measure of the effect of these drugs. It is at least as sensitive a measure as analgesia. By using D(—)-levorphanol and its L(+)-isomer, a high degree of stereospeificity has been demonstrated. A number of criteria have been applied to show that the running fit is a typical pharmacologic effect of this family of drugs. The development of tolerance has been studied with repeated injections of levorphanol, and the loss of tolerance has been studied upon discontinuance of the drug. The rate of onset of tolerance and the degree of tolerance eventually attained are determined by the frequency of administration of a constant drug dose or by the size of the dose at a fixed interval. The duration of drug administration is irrelevant. Tolerance is revisible at a rate roughly the same as the rate of onset, and recovery of sensitivity to levorphanol is complete. Subsequent cycles of onset and offset of tolerance are indistinguishable from the first.

GOLDSTEIN, A., SHEEHAN, P. and GOLDSTEIN, J. Unsuccessful attempts to transfer morphine tolerance and passive avoidance by brain extracts. Nature 233 (531.5): 126-129 (September, 1971)

GONZALEZ, L.P., ALTSHTHULER, H.L. and BURCH, N.R. Period analytic descriptors of the effects of psychotropic drugs in the subhuman primate. Proceedings of the Society for Neurosciences 3(6): 226 (1973)

Period analysis of the electroencephalogram (EEG) has been used to evaluate the human EEG, but only to a limited degree in animal experiments. These studies were designed to establish its efficacy as a means to evaluate the effects of centrally active drugs on the electrical activity of the brain and behavior. Three rhesus monkeys were used in this study. They were restrained in monkey chairs and placed in a quiet, shielded room for the experiments. Intravenous saline injections were used for control studies. Intravenous doses of pentobarbitol (2.0-20.0 mg/kg), morphine sulfate (0.5-5.0 mg/kg) or chlorpromazine (1.0-10.0 mg/kg) were administered to each animal according to a modified Latin Square design. The EEG was continuously recorded for two hours after each dose and the analogue data base reduced by computer-based period analysis. Major emphasis was placed on the changes observed in the minor period. All three compounds decreased the major and intermediate period counts below saline controls in a dose-related fashion. All three drugs induced substantial and distinctive changes in the second derivative function, the minor period, Minor period counts were generally reduced for the higher doses of each drug, and lower doses occasionally increased minor period counts at upper frequency bands. The data demonstrate the efficacy of the period analysis technique in distinguishing between different psychoactive drugs and serve to provide data base for studies of the EEG correlates of the behavioral changes induced by these and similar compounds.

GREEN, J.P., DRESSLER, K.P. and KHAZAN, N. Mescaline-like activity of 2-amino-7-hydroxytetralin. Life Sciences 12 (part I) 475-479 (1973)

2-Amino-7-hydroxytetralin has sleep effects in rats like mescaline and D-LSD, and it showed cross-tolerance with mescaline, as did D-LSD. These properties had been predicted by total valence electron calculations.

GREEN, T.K. and HARVEY, J.A. Enhancement of amphetamine action after interruption of ascending serotonergic pathways. The Journal of Pharmacology and Experimental Therapeutics 190: 109-117 (1974)

Large lesions, producing 60 to 90% destruction of the medial forebrain bundle (MFB) and a 60 to 84% decrease in telencephalic content of scrotonin, also preduced a 3-fold enhancement of amphetamine action as measured by increased rates of responding on a variable-interval 60-second schedule of reinforcement. These lesions had no effect on the action of chlorpromazine. Smaller lesions, producing 10 to 50% destruction of the MFB and a 1 to 59% decrease in serotonin, had no effect on amphetamine action. The correlation between the decrease in serotonin and the enhanced action of 1 mg/kg of amphetamine sulfate was 0.81 for 16 rats with MFB lesions. Lesions in the septal area, central gray, dorsomedial tegmentum or ventrolateral tegmentum produced only small (12-19%) decreases in serotonin and had no effect on amphetamine action. The enhanced action of amphetamine after MFB lesions could not be attributed to base-line rates of lever pressing, water consumption, body weight or changes in catechoamines. It was concluded that the serotonergic system plays an important role in determining the magnitude of amphetamine effects on behavior.

GROVER, T., PIETLE, L.H. and MANIAN, A. Hydroxylation of 7-hydroxy-chlorpromazine by mushroom tyrosinase. Proceedings of the Third International Conference on Phenothiazines. New York: Raven Press, 1973.

GROVES, P.M. and REBEC, G.V. The action of d-amphetamine on spontaneous activity in the caudate nucleus and reticular formation of the rat. Journal of Behavioral Biology 11(1): 33-47 (1974)

Dextro-amphetamine sulfate injected intraperitoneally in paralyzed, locally anesthetized rats, resulted in a biphasic alteration in spontaneous activity in the caudate nucleus. An initial dose-dependent potentiation of activity occurs 5-10 min after injection followed by a prolonged dose-dependent depression of activity which may last as long as several hours. Similar injections result in a different time-course of alterations in the mesencephalic reticular formation consisting of a prolonged increase followed by a depression of spontaneous activity. Spontaneous activity in the caudate nucleus was relatively unaffected by mephentermine sulfate, a peripheral sympathominletic. The depression of activity produced by amphetamine could be reversed by haloperidol, a dopaminergic blocking agent. Haloperidol injected alone produced a transient potentiation of activity followed by a return to control firing rate. These results provide electrophysiological support for the inhibitory synaptic function of dopamine in the caudate-putamen and for the alleged action of amphetamine and haloperidol at these sites. Both the differential biochemical and neurophysiological effects of amphetamine on the caudate nucleus and reticular formation may have functionally significant behavioral consequences.

GROVES, P.M., REBEC, G.V. and HARVEY, J.A. Alteration of the effects of d-amphetamine on neuronal activity in the caudate nucleus following lesions of the nigrostriatal bundle. Neuropharmacology (in press)

GRUBB, M.N. and BURKS, T.F. Modification of intestinal stimulatory effects of 5-hydrorytryptamine by adrenergic amines, prostaglandin E_1 and theophylline. The Journal of Pharmacology and Experimental Therapeutics 189(2): 476 (1974)

A study was designed to examine the intestinal stimulatory effects of 5-hydroxytryptamine (5-HT) in the presence of three types of drugs which are known to decrease intestinal motility. Dog isolated intestinal segments were perfused via thevasculature with Krebs-bicarbonate solution with or without drugs which depress motility: adrenergic amines, prostaglandin El and theophylline. The excitatory agonists tested were 5-HT, bethanechol and dimethylphenylpiperazinium (DMPP), Isoproterenol (1 and 5 mu-g/ml) shifted the 5-HT dose-response curve to the right but did not affect intestinal contractions produced by the cholinergic agonists, bethanechol and DMPP. Prostaglandin El (1 mu-g/ml) did not alter responses to bethanechol, but caused a slight decrease in responses to DMPP. The prostaglandin shifted the 5-HT dose-response curve to the right. Theophylline (180 mu-g/ml) had no effect on responses to bethanechol or DMPP but produced a shift to the right in the dose-response curve for 5-HT. Norepinephrine (0.1 and 0.2 mu-g/ml) had no effect on responses to bethanechol, but produced shifts to the right in dose-response curves for DMPP and 5-HT. Methoxamine (10 and 50 mu-g/ml) caused effects similar to those produced by norepinephrine. These data indicate that beta adrenergic agonists, prostaglandin El and theophylline, which have in common the ability to increase intestinal cyclic adenosine monophosphate (cyclic AMP), antagonize motility responses to 5-HT but have little or no effect on motility responses to cholinergic agonists. The effect of norepinephrine on DMPP can be explained in terms of alpha adrenergic receptor actions since methoxamine had similar effects on DMPP responses. It is hypothesized that 5-HT produces contractions of intestinal smooth muscle by somehow lowering intracellular levels of cyclic AMP or by blocking cyclic AMP inhibitory effects.

HAAVIK, C.O. and HARDMAN, H.F. The effect of tetrahydrocannabinols on body temperature. Proceedings of the Fifth International Congress on Pharmacology. Satellite Sympozium on the Pharmacology of Thermoregulation, San Francisco, 1972.

HAHN, D.L. and GOLDSTEIN, A. Amounts and turnover rates of brain proteins in morphine-tolerant mice. Journal of Neurochemistry 18: 1887-1893 (1971)

For abstract, see Section II. Drug Chemistry and Metabolism.

HAIGLER, H.J. and AGHAJANIAN, G.K. Lysergic acid diethylamide and serotonin: A comparison of effects on serotonergic neurons and neurons receiving a serotonergic input. The Journal of Pharmacology and Experimental Therapeutics 188(3): 688-699 (1974)

Lysergic acid diethylamide (LSD) administered systemically to rats has been shown to reversibly inhibit serotonin (5-HT) containing neurons of the raphe nuclei (serotonergic neurons). This inhibition could be due to either a direct effect or an indirect action via a postsynaptic neuronal feedback loop. To compare the responsivity of serotonergic neurons and postsynaptic neurons to LSD, raphe neurons and neurons in 4 areas (ventral lateral geniculate, amygdala, optic tectum and subiculum) with an identified 5-HT input from the midbrain raphe nuclei were tested for their response to microiontophoretically ejected and systemically administered LSD. Compared to the raphe, cells in these postsynaptic areas were relatively insensitive to microiontophoretic LSD Raphe cells could be totally inhibited by LSD at ejection currents too low to have any effect on the postsynaptic neurons. In contrast, 5-HT was very nearly equipotent in depressing the firing of the presynaptic (raphe) cells and the postsynaptic cells. To determine if LSD has any indirect inhibitory effect upon raphe neurons via a neuronal feedback, LSD was administered to animals with a mesencaphalic-diencephalic transection. In these animals LSD still produced inhibition of raphe cells at doses comparable to those in control animals. It is concluded: 1) Raphe neurons are more sensitive to inhibitory effects of LSD than are postsynaptic neurons (i.e., neurons receiving an identified 5-HT input); and 2) the inhibitory effect of low doses of LSD on the presynaptic (raphe) cells is caused by a direct inhibitory action rather than an indirect action via a neuronal feedback.

HARRIS, L.S., DEWEY, W.L., SPAULDING, T.C., LEVY, J.A. and PLAINTIDOSI, S. Recent studies on the development of tolerance and physical dependence in rodents. Presented at the American Chemical Society Meeting, Rochester, New York, October 15, 1973.

HARRIS, L.S., MUNSON, A.F., FRIEDMAN, M.A. and DEWEY, W.L. Retardation of tumor growth by delta-9-tetrahydrocanabinol. The Pharmacologist 390 (1974)

Oral administration of delta-9-THC (25-100 mg/kg) bound to bovine serum albumin was investigated for potential antitumor action on Lewis lung carcinoma. BDG_1 male mice were inoculated with 10^6 tumor cells into right hind leg and treated daily for 10 days beginning 24 hrs. after tumor implantation. On day 12 of this experiment , delta-9-THC retarded primary tumor growth 48%, 72% and 75% at 25, 50 and 100 mg/kg, respectively. Mice receiving 100 mg/kg survived 36% longer than control as compared to 45% for the cyclophosphamide positive control. Mice treated for 20 days showed slightly less inhibition of primary tumor growth with no increase in lifespan. In this study, cannabinol, at the same doses at delta-9-THC. administered for 20 days showed slightly less activity on tumor growth and did not prolong survival time. In preliminary mechanismistic studies, delta-9-THC administered acutely, inhibited ^3H thymidine uptake into tumor DNA but not in brain, testes, spleen or bone marrow. Twenty-four hours after a single oral gavage of 400 mg/kg delta-9-THC, DNA synthesis was reduced 75%. DNA synthesis was not significantly altered in primary tumor or tissues of mice similarly treated for 20 days.

HARVEY, J.A., editor. Behavioral Analysis of Drug Action. Glenview, Illinois: Scott, Foresman and Company, 1971.

HARVEY, J.A. and LINTS, C.E. Lesions in the medial forebrain bundle: Relationship between pain sensitivity and telencephalic content of serotonin. Journal of Comparative and Physiological Psychology 74:28-36 (1971)

Lesions in the medial forebrain bundle (MFB) or injection of p-chlorophenylalanine decreased brain content of serotonin and decreased jump thresholds in rats. The effects of lesion and drug were not additive indicating that a common system was being affected by both procedures. Injection of 75 mg/kg DL-5-hydroxytryptophan into rats with lesions returned both the jump threshold and serotonin content to normal values. The correlation between jump threshold and telencephalic serotonin was +.80. Brainstem serotonin was not related to jump threshold. Decreases in jump threshold were interpreted as indicating an increased pain sensitivity. It was concluded that this behavioral effect of the MFB lesion is secondary to the effects of the lesion on serotonin content of the telencephalon.

HARVEY, J.A., SCHLOSBERG. A.J. and YUNGER, L.M. Behavioral correlates of serotonin depletion. Federation Proceedings (in press)

HARVEY, J.A., SCHLOSBERG, A.J. and YUNGER, L.M. Effect of p-cpand brain lesions on pain sensitivity and morphine analgesia in the rat. Advances in Biochemical Psychopharmacology, Vol. 10. Edited by E. Costa, G. L. Gessa and M. Sandler. New York: Raven Press, 1974.

HASSELAGER, E., ROLINSKI, Z. and RANDRUP, A. Specific antagonism by dopamine inhibitors of items of amphetamine induced aggressive behaviour. Psychopharmacologia 24: 485-495 (1972)

d-Amphetamine in a dose of 15 mg/kg elicits both aggressive activities and stereotyped sniffing, licking and biting of the cage in mice. A selective inhibition of the aggressive activities (without general sedation of the mice) was obtained by small doses of the neuroleptics spiramide and trifluperazine, indicating that this behaviour was mediated by increased activity of dopmaine in the brain. This indication was supported by experiments with noradrenaline blocking agents and inhibitors of the synthesis of dopamine and noradrenaline.

HARVEY, J.A. and YUNGER, L.M. Relationship between telencephalic content of serotonin and pain sensitivity. Serotonin and Behavior. Edited by J. Barchus and E. Usdin. New York: Academic Press, 1973.

HENDERSON, A., NEMES, G., GORDON, N.B. AND ROOS, L. Sleep and narcotic tolerance. Psychophysiology 7(2): 346-347 (September, 1970)

HENDLEY, E.D., TAYLOR, K.M. and SNYDER, S.H. ^{3}H-normetanephrine uptake in rat brain slices. Relationship to extraneuronal accumulation of norepinephrine. European Journal of Pharmacology 12: 167-179 (1970)

^{3}H-Normetanephrine accumulation in slices of rat brain was characterized and contrasted with ^{3}H-norepmephrine accumulation. Initial rates of normetanephrine uptake were very rapid; accumulated amine was not bound to particulate fractions and was easily washed out of the tissues. Unlike norepinephrine uptake, normetanephrine accumulation was unaffected by reserpine, was not stereospecific and was less affected by omission of glucose or sodium than was norepinephrine uptake. The cerebral cortex was the region of greatest normetanephrine accumulation whereas the corpus striatum accumulated norepinephrine to highest tissue: medium ratios. Several features of normetanephrine uptake in brain resembled both $Uptake_2$ of norepinephrine in heart and the extraneuronal uptake of norepinephrine in cocanized hearts. In rat brains in which the catecholamine nerve terminals were destroyed by intraventricularly administered 6-hydroxydopamine. endogenous norepinephrine was markedly reduced; ^{3}H-norepinephrine accumulation by slices was decreased, and displayed characteristics more like normetanephrine uptake than like norepinephrine uptake in control animals.

HERNDON. B.L., BAEDER, D.H. and RINGLE, D.A. Antagonism of morphine analgesia by morphine-pellet implanted rabbit serum. Federation Proceedings (in press)

Studies reported by us earlier and confirmed in another laboratory have shown that repeated s.c. implantation of rabbits with pellets of morphine and certain other narcotics evokes production of a serum component that shows increased drug binding ability. This component has the characteristics of an immunoglobulin.

In the study reported here, rabbit anti-morphine pellet serum (anti-MP) was given i.v. to rats at a dose level equal to 20% of their blood volume. For comparison, two other groups of rats were given either an antiserum against a morphine-protein conjugate or serum from placebo pellet-implanted rabbits. The effects on morphine analgesia in these three rat groups were tested on a hot plate following a 5 mg/kg dose of morphine s.c. Anti-MP serum and the antiserum to the morphine-protein conjugate both significantly attenuated the analgesic response to morphine on the first day after serum treatment. Subsequent tests on the same animals up to 6 weeks after serum injection showed no differences in response among the three rat groups after the second day, although a measurable level of rabbit gamma globulin remained in the serum of most rats one month after injection.

HILL, H.F. and HORITA, A. Inhibition of (+)-amphetamine hyperthermia by blockade of dopamine receptors in rabbits. Journal of Pharmacy and Pharmacology 23: 715 (1971)

HILL, H.F. and HORITA, A. A pimozide-sensitive effect of apomorphine on body temperature of the rabbit. Journal of Pharmacy and Pharmacology 24: 490 (1972)

HILLER, J.M., PEARSON, J. and SIMON, E.J. Distribution of stereospecific binding of the potent narcotic analgesic etorphine in the human brain: Predominance in the limbic system. Research Communications in Chemical Pathology and Pharmacology 6(3): 1052-1061 (November, 1973)

Homogenates of human brain tissue obtained at autopsy exhibit stereospecific binding of the potent narcotic analgesic ^{3}H-etorphine. Analysis of binding levels in 39 anatomic sites shows a wide range of regional variation but good consistency for the same area in different brains. Most sites with the highest binding activity lie within the limbic system. Evidence in the literature supporting the significance of the limbic system in responses to opiates is examined in the light of these findings.

HILLER, J.M. and SIMON, E.J. Inhibitions by levorphanol of the induction of acetylcholinesterase in a mouse neuroblastoma cell line. Journal of Neurochemistry 20: 1789-1792 (1973)

HIRSCHHORN, I.D. and WINTER, J.C. Mescaline and lysergic acid diethylamide (LSD) as discriminative stimuli. Psychopharmacologia 22: 64-71 (1971)

The observation that a particular drug state may acquire the properties of a discriminative stimulus is explicable on the basis of drug-induced interoceptive cues. The present investigation sought to determine (a) whether the hallucinogens mescaline and LSD could serve as discriminative stimuli when either drug is paired with saline and (b) whether discriminative responding would occur when the paired stimuli are produced by equivalent doses of LSD and mescaline. In a standard two-lever operant test chamber, rats received a reinforcer (sweetened milk) for correct responses according to a variable interval schedule. All sessions were preceded by one of two treatments; following treatment A, only responses on lever A were reinforced and, in a similar fashion, lever B was correct following treatment B. No responses were reinforced during the first five minutes of a daily thirty-minute session. It was found that mescaline and LSD can serve as discriminative stimuli when either drug is paried with saline and that the degree of discrimination varies with drug dose, When equivalent doses of the two drugs were given to the same animal, no discriminated responding was observed. The latter finding suggests that mescaline and LSD produce qualitatively similar interoceptive cues in the rat.

HITZEMANN, R.J., HO, I.K., CHO, T. M. and LOH, H.H. Narcotic tolerance and dependence and serotonin turnover. Science 178: 645-647 (1972)

HITZEMANN, R.J. and LOH, H.H. Effect of morphine on the transport of dopamine into mouse brain slices. European Journal of Pharmacology 21: 121-129 (1973)

For abstract, see Section II. Drug Chemistry and Metabolism.

HO, B.T., ESTEVEZ, V.S. and ENGLERT, L.F. Effect of repeated administration on the metabolism of (-)-delta-9-tetrahydrocannabinols in rats. Research Communications in Chemical Pathology and Pharmacology 5(1): 215-218 (January, 1973)

For abstract, see Section II. Drug Chemistry and Metabolism.

HO, I.K. Effect of pharmacological manipulation on pentobarbital response. Proceeding of the Western Pharmacological Society (in press)

The present studies describe the effect of pharmacological manipulations which alter the functional state of putative neurotransmitters or neurohormones on the responses of pentobarbital. As judged by sleeping time, the results show that aminooxyacetic acid (an inhibitor of GABA transaminase), alpha-methyl tyrosine (an inhibitor of tyrosine hydroxylase) and pargyline (an inhibitor of monoamine oxidase) potentiated the pentobarbital effect on sleeping time. However, p-chlorophenylalanine (an inhibitor of tryptophan hydroxylase) antagonized the effect.

HO, I.K. LOH, H.H. and WAY, E.L. Cyclic adenosine monophosphate antagonism of morphine analgesia. The Journal of Pharmacology and Experimental Therapeutics 185: 336-346 (1973)

The administration of cyclic adenosine 3', 5'-monophosphate (cAMP) intracerebrally or intravenously antagonized morphine analgesia in nontolerant and tolerant mice. The cAMP surrogates dibutyryl cAMP, a phosphodiesterase-resistant cAMP analog, and theophylline, a phosphodiesterase inhibitor, acted in a similar manner. The antagonism of morphine effects by all three compounds persisted for at least 24 hours and may have lasted for 48 hours. Elevation of brain biogenic amines by monoamine oxidase inhibition with pargyline reversed the antagonistic effects of cAMP on morphine analgesia. Increasing brain dopamine with L-dopa did not prevent cAMP antagonism of morphine analgesia. Increasing brain serotonin with tryptophan not only failed to reverse the effect of cAMP, but also appeared to enhance the cAMP response. However, elevation of norepinephrine with dihydroxyphenylserine did reverse the antagonistic effect of cAMP. It is concluded, therefore, that norepinephrine is more important for the reversal of cAMP antagonism of morphine analgesia than either dopamine or serotonin.

HO, I.K., LOH, H.H. and WAY, E.L. Effects of cyclic 3', 5'-adenosine monophosphate on morphine tolerance and physical dependence. The Journal of Pharmacology and Experimental Therapeutics 185(2): 347-357 (1973)

The administration of cyclic 3', 5'-adenosine monophosphate (cAMP) antagonized the analgetic response of morphine in both nontolerant and tolerant mice and also accelerated the development of tolerance to and physical dependence on morphine induced by morphine pellet implantation. Tolerance enhancement by cAMP was evidenced by the increased amount of morphine to produce analgesia and acceleration in dependence by the decrease in the amount of naloxone to induce precipitated withdrawal jumping after cAMP pretreatment. Further evidence that cAMP accelerated dependence development on morphine was evidenced by the fact that cAMP increased the loss in body weight that occurred after abrupt morphine withdrawal. Cycloheximide prevented the accelerating effect of cAMP on tolerance and physical dependence development.

HO, I.K., LOH, H.H. and WAY, E.L. Influence of GABA on morphine analgesia, tolerance and physical dependence. Proceedings of the Western Pharmacological Society 16: 4-7 (1973)

HO, I.K., SUTHERLAND, V. C. and LOH, I-L H. A model for the rapid development of tolerance to barbiturates. Research Communications in Chemical Pathology and Pharmacology 6(1): 33-46. (July, 1973)

For abstract, see Section I. Methodology of Drug Research.

HO, I.K., YAMAMOTO, I., LOH, H.H. and WAY, E.L. Enhancement of pentobarbital responses after morphine addiction. The Pharmacologist 16(2): 193 (1974)

For abstract, see Section II. Drug Chemistry and Metabolism.

HODGSON. J.R., BRISTOW, R.L. and CASTLES, T.R. Repression of RNA transcription during the development of analgesic tolerance to morphine. Nature 248(5450): 761-763 (April 19, 1974)

For abstract, see Section II. Drug Chemistry and Metabolism.

HOLLISTER, A.S., BREESE, G.R. and COOPER, B.R. Comparison of tyrosine hydroxylase and dopamine-beta-hydroxylase inhibition with the effects of various 6-hydroxydopamine treatments on d-amphetamine induced motor activity. Psychopharmacologia 36: 1-16 (1974)

The significance of central noradrenergic and dopaminergic neural systems for the locomotor stimulant effects of d-amphetamine were investigated in rats with depletions of norepinephrine, dopamine, or both catecholamines produced by treatment with either reserpine. L-alpha-methyl-tyrosine (alpha-MPT), 6-hydroxydopamine (6-OHDA), or the dopamine-beta-hydroxylase inhibitor 1-phenyl-3 (2-thiazolyll-2-thiourea (U-14,624). In animals pretreated with reserpine, amphetamine-stimulated locomotor activity was blocked by alpha-MPT but not by U-14,624 when amphetamine was given 1 h after these catecholamine synthesis inhibitors. In rats with chronic depletions of brain norepinephrine, dopamine, or both catecholamines produced by different 6-OHDA treatments, both amphetamine-stimulated motor activity and sterotyped behavior were antagonized by treatments reducing dopamine or both catecholamines but not in animals in which brain norepinephrine was reduced. Results are consistent with the view that the locomotor stimulation and stereotyped behaviors produced by d-amphetamine are dependent upon functional dopaminergic neural systems in-brain.

HOLLISTER, L.E. Cannabidiol and cannabinol in man. Experientia 29: 825-826 (1973)

HOLLISTER, L.E. Human pharmacology of marihuana: What next? Psychopharmacology Sexual Disorders and Drug Abuse. Edited by T. A. Ban, J.R. Boissier, G.J. Gessa, H. Heimann, L. Hollister, H.E. Lehmann, I. Munkvad, H. Steinberg, F. Sulser, A. Sundwall and 0. Vinar. Amsterdam, the Netherlands: North-Holland Publishing Company, 1973. Pp. 705-706.

HOLLISTER, L.E. Interactions in man of delta-9-tetrahydrocannabinol. Clinical Pharmacology and Therapeutics 15(1): 18-21 (1974)

The interaction of alphamethylparatyrosine (AMPT) and delta-9-tetrahydrocannabinol (THC) was studied in three separate experiments, two giving THC orally, one adminstering it intravenously. Pretreatment with doses of 2.0 to 4.0 gm of AMPT produced no major qualitative or quantitative change in the effects of THC. Some accentuation of the total intensity of THC was apparent in each of these experiments, but one could not be certain whether this difference was due to additive pharmacologic effects or diminished catecholamine concentrations in brain. It would appear that mental effects of THC are not mediated primarily through catecholamines, but rather by the balance between the concentrations of these amines and others, such as acetylcholine or serotonin.

HOLLISTER, L.E. Tetrahydrocannabinol isomers and homologues: Contrasted effects of smoking. Nature 227(5261): 968 (August, 1970)

HOLLISTER, L.E. and GILLESPIE, H.K. Delta-8- and delta-9-tetrahydrocannabinol. Clinical Pharmacology and Therapeutics 14(3): 353-357 (1973)

Delta-8-tetrahydrocannabinol (THC) has activity in man similar to that of its double-bond isomer, delta-9-THC. Its relative potency to the other isomer, as judged following both oral and intravenous administration, is 2.3. Intravenous administration of ethanolic solutions of cannabinoids in clinically active doses is feasible and desirable for experimental purposes. A range of doses of 1 to 6 mg of delta-9-THC intravenously produced a wide spectrum of cannabis-like effects. Relatively simple clinical techniques clearly detect cannabis-like activity in man, making both qualitative and quantitative comparisons of unknown materials with delta-9-THC feasible.

HOLLISTER, L.E., KANTER, S.L. and DRONKERT, A. Antidiureses in man following lysergic acid diethylamide and mescaline. Behavioral Neuropsychiatry 2: 50 (1970)

An antidiuretic effect following oral doses of 1. 5 to 2 mcg/kg of lysergic acid diethylamide (LSD) was produced in 10 of 14 subjects. As compared with a control day during which a water load was administered, LSD decreased urine formation, decreased free water clearance, and increased urine osmolality. These changes occurred promptly and lasted four hours or more. Determination of serum osmolality and sodium content, or urinary excretion of sodium and chloride, was of no help in demonstrating an antidiuretic effect. Similar changes in urine formation were noted after doses of 5 to 6 mg/kg of mescaline, effects being more constant and profound. Attempts to relate the degree of antidiuresis with another measure of physiologic stress, the rise in plasma free fatty acids, or clinical indicators of stress as reported by subjects, were unsuccessful.

HOLLISTER, L.E., MacNICOL, M.F. and GILLESPIE, H.K. An hallucinogenic amphetamine analog (DOM) in man. Psychopharmacologia 14: 62-73 (1969)

The amphetamine analog, 2, 5-dimethoxy-4-methylamphetamine (DOM), was studied in 18 volunteer subjects given single doses ranging from 2 to 14 mg. The former was a threshold dose, with definite psychotomimetic effects being evident from doses over 5 mg. The clinical syndrome greatly resembled that of the LSD-mescaline-psilocybin series of drugs, including its time-course. Somewhat more sedation was produced by DOM than would have been expected from the others, despite concomitant evidence of peripheral sympathetic stimulation. Just as with the other drugs, DOM increased plasma free fatty acids, decreased phosphorus and creatinine clearance, decreased circulating eosinophils and had little effect on catecholamine excretion. Performance of psychometric tests was impaired. Chlorpromazine treatment concurrently was found to attenuate the reaction. Tolerance rapidly developed when the drug was used chronically by patients.

HOLLISTER, L.E., MOORE, F., KANTER, S. and NOBLE, E. Delta-l-tetrahydiocannabinol, synhexyl and marijuana extract adminstered orally in man: Catechoiamine excretion, plasma cortisol levels and platelet serotonin content. Psychopharmacologia 17: 354-360 (1970)

Measurements of catecholamine excretion, plasma cortisol and platelet serotonin concentration were done in the course of experiments in which human volunteers were given sizable oral doses of delta-tetrahydrocannabinol, synhexyl or marijuana extracts. A transient rise in epinephrine excretion was observed following THC but seemed best explained by the anticipatory stress of the experiment or the rapid onset of unfamiliar symptoms. A decreased turnover of catecholamines or a shift in the degradative pathways of catecholamines from the oxidative to the reductive route was suggested by the decrease in VMA excretion following synhexyl. Plasma cortisol was unchanged except in the presence of clinically obvious psychological distress on the part of the patient. Platelet serotonin was unchanged.

The lack of major effects of marijuana-like drugs on these and other clinical measurement of stress corroborates the clinical observation that drugs of this type seem to be less stressful than the usual psychotomimetics. The pronounced euphoriant and sedative effect of marijunana may ameliorate the stress of the psychotomimetic experience.

HOLLISTER, L.E., RICHARDS, R.K. and GILLESPIE, H.K. Comparison of tetrahydrocannabinol and synhexyl in man. Clinical Pharmacology and Therapeutics 9(6): 783-791 (November-December, 1968)

A synthetic isomer of tetrahydrocannabinol (1-delta'-3,4-transtetrahydrocannabinol), believed to be identical to the most active naturally occurring THC, was compared with a semisynthetic THC-like compound, synhexyl. Sixteen volunteer subjects received THC in doses ranging from 341 to 946 mu-g per kilogram (median 581). Thirteen subjects received synhexyl in doses. ranging from '633 to 2,666 mu-g per kilogram (median 1.370). Clinical syndromes from the 2 drugs were similar, although synhexyl was slower in onset and only about one third as potent. The clinical effects resembled those of psychotomimetics such as LSD, at least at the higher doses. These drugs differed from LSD in the following respects: sedation was prominent; euphoria was longer lasting; dreamlike sequences more pronounced; and physiological and biochemical effects were somewhat different, especially in the absence of sympathomimetic effects.

HOLLISTER, L.E. and TINKLENBERG. J.R. Subchronic oral doses of marihuana extract. Psychopharmacologia 29: 247-252 (1973)

For abstract, see Section II. Drug Chemistry and Metabolism.

HOLTZMAN, S.G. and JEWETT, R.E. Interactions of morphine and nalorphine with physostigmine on operant behavior in the rat. Psychopharmacologia 22: 384-395 (1971)

Morphine and nalorphine were tested alone and in combination with physostigmine (0.0625 mg/kg) in rats trained under a continuous avoidance schedule with an escape contingency. When tested alone, nalorphine increased avoidance rate in doses up to 32 mg/kg but exerted no other effects. Morphine, 1 mg/kg, increased avoidance response rate while higher doses produced a graded depress ion of all behavior. In the presence of physostigmine. nalorphine produced a well-defined graded depression of avoidance responding and increased the number of shocks received by the animals over a 16-fold dose range. Physostigmine failed to potentiate the prominent depressant effects of morphine in the same test situation. The finding that in the presence of cholinesterase'inhibition nalorphine acts as a depressant of operant behavior in the rat supports existing evidence that cholinergic mediation should be considered as a factor in some of the actions of strong analgesics.

HOLTZMAN, S.G. and JEWETT, R.E. Some actions of pentazocine on behavior and brain monoamines in the rat. The Journal of Pharmacology and Experimental Therapeutics 181(2): 346 (1972)

The effects of pentazocine, a weak narcotic-antagonist analgesic, were studied on operant behavior (continuous avoidance schedule), locomotor activity and brain nonoamines in the rat. Operant behavior was increased in a graded manner by 2 to 16 mg/kg of pentazocine and decreased by 32 mg/kg. Both stimulant and depressant effects were antagonized by the potent narcotic antagonist naloxone (8 mg/kg). Pentazocine, 8 to 64 mg/kg, produced a graded increase in locomotor activity which was not prevented by as much as 16 mg/kg of naloxone. Stimulation of locomotor activity was blocked by alpha-methyltyrosine, an inhibitor of catecholamine synthesis. The total brain content of norepinephrine, dopamine, and serotonin was reduced by pentazocine; turnover rates were not affected. The depletion of the catecholamines was $2\frac{1}{2}$-$3\frac{1}{2}$ times greater than that of serotonin. Morphine, in doses as high as 256 mg/kg, caused a much smaller reduction in brain norepinephrine than did pentazocine and elevated brain levels of dopamine. Naloxone (16 mg/kg) failed to block the effects of pentazocine on brain monoamines but did block those of morphine. These findings have been interpreted as follows: 1) the actions of pentazocine on operant behavior appear to be independent of its effects on brain monoamines; 2) stimulation of locomotor activity by pentazocine may be related to the release of brain monoamines; and 3) some of pentazocine's agonistic effects are mediated by mechanisms distinct from those which mediate the actions of morphine.

HOLTZMAN. S.G. and JEWETT, R.E. Stimulation of behavior in the rat by cyclazocine: Effects of naloxone. The Journal of Pharmacology and Experimental Therapeutics 187(2): 380 (1973)

The actions of cyclazocine, a potent analgesic with mixed agonist and narcotic antagonist properties, were evaluated on two distinct types of behavior in the rat: lever pressing maintained under a continuous avoidance schedule and locomotor activity. The effects of cyclazocine on the total brain content of norepinephrine, dopamine and serotonin were also examined. Dose-response curves were determined for cyclazocine alone, then redetermined with concomitant administration of naloxone at two dose levels. d-Amphetamine was also tested alone and with naloxone on avoidance behavior. Cyclazocine increased avoidance responding and locomotor activity in a graded manner over a broad range of doses. Both behaviors were disrupted by the highest doses of cyclazocine. Cyclazocine lowered brain catecholamine levels slightly. Naloxone, inactive in all procedures, attenuated the stimulant and disruptive effects of cyclazocine on avoidance behavior, but failed to block cyclazocine's effects on locomotor activity and brain catecholamine levels. Naloxone reduced the rate-increasing effect of d-amphetamine on avoidance responding and enhanced the disruption of avoidance-behavior produced by a high dose of that drug. These findings are consistent with the view that the agonistic component of action of some narcotic antagonists is mediated by several mechanisms, at least one of which is not blocked by naloxone. The interaction between naloxone and d-amphetamine emphasizes the need for further evaluation of possible interactions between narcotic antagonists and psychoactive drugs of classes other than the opioid.

HORITA, A. Pharmacological aspects of the unnatural amino acids and amines. Federation Proceedings 30(3): 857-858 (May-June, 1971)

HORITA, A. and CARINO, M.A. Modification of the toxic actions of 1-tryptophan by pargyline and p-chlorophenylalanine. Biochemical Pharmacology 19: 1521 (1970)

HORITA, A., CLINESCHMIDT, B.V. and McMONIGLE, J.J. The role of metabolism in the action of some monoamine oxidase inhibitors. Excerpta Medica International Congress Series No. 180. Present Status of Psychotropic Drugs. Amsterdam, the Netherlands: Excerpta Medica Foundation, 1968.

HORITA, A. and HAMILTON, A.E. The effects of DL-alpha-methyltyrosine and L-dopa on the hyperthermic and behavioral actions of LSD in rabbits. Neuropharmacology 12: 471-476 (1973)

Lysergic acid diethylamide (LSD) in relatively small doses produces in rabbits a dose-related hyperthermia and behavioral excitation.

After a 24 hr pretreatment with DL-alpha-methyl-p-tyrosine (alpha-MT), the LSD hyperthermia is no longer dose related. With lower doses of LSD it is potentiated, and with higher doses attenuated. The behavioral actions of LSD are attenuated at all dose levels.

The administration of L-dihydroxyphenylalanine (L-DOPA) restores the behavioral action of LSD in alpha-MT-pretreated rabbits. Prior administration of the dopamine-beta-hydroxylase inhibitor, sodium diethyldithiocarbamate (DEDC) was ineffective in blocking the restorative action of L-DOPA.

Analyses of brainstem catecholamines indicate that under the conditions of this study alpha-MT markedly depletes brain norepinephrine (NE) and dopamine (DA). L-DOPA restores DA and partially restores NE levels to control values. In animals pretreated with DEDC the effect of L-DOPA treatment on brainstem DA is enhanced with only slight increases in NE levels.

HORITA, A. and HAMILTON, A.E. On the hyperthermic action of 2, 5-dimethoxy-4-methyl-amphetamine (DOM). Proceedings of the Western Pharmacological Society 15: 104 (1972)

In earlier studies we described the hyperthermic action of d-amphetamine in rabbits as differing from that produced in rats because of the lack of antagonism by beta-blocking agents, while the antidopamine compound, pimozide, was highly effective in attenuating this response. These and other evidence indicated the involvement of a dopaminergic link in the amphetamine-induced hyperthermia in the rabbit.

In the present report we describe the nature of the temperature response of rabbits to the hallucinogenic amphetamine derivative, 2.5-dimethoxy-4-methyl-amphetamine (DOM). In doses above 0.05 mg/kg DOM exerts a dose-dependent pyretogenic effect which is characterized by a peak response at 2-3 hr and with a duration of some 8-10 hr. This is in contrast to the effect of d-amphetamine which peaks at 0.5-1.0 hr and lasts for only 2-3 hr. Above 1.0 mg/kg DOM exerts in some animals lethal hyperthermia with temperatures rising to above 430-440. In addition to the hyperthermia, animals with sublethal doses of DOM exhibit some changes in gross behavior, such as piloerection, increased respiration, and vaso-constriction of ear vessels, but it produces none of the increased behavioral or locomotor activity as seen with amphetamine.

When animals pretreated with pimozide (4 mg/kg, 3 hr previously) are injected with 0.5 mg/kg of DOM the hyperthermia is only slightly decreased from that of control DOM rabbits. However, rabbits pretreated with cinanserin HCl (5-10 mg/kg, 30 min previously) exhibit a greatly attenuated response to DOM.

These preliminary results indicate that, while the amphetamine-induced hyperthermia in rabbits is mediated via a dopaminergic mechanism, the response seen with DOM resembles that produced by LSD and other indole amine hallucinogens. This interpretation is consistent with the findings of Wolbach et al. on the development of a cross-tolerance between the psychotomimetic actions methoxylated phenethylamines and LSD, which in turn suggests a common site of action for the two types of drugs.

HORITA, A. and HAMILTON, A.E. Potentiation of the central actions of 5-hydroxytryptophan in rabbits by DL-alpha-hydrazino-alpha-methyldopa. Journal of Pharmacy and Pharmacology 22: 389 (1970)

HORITA, A. and HILL, H.F. Hallucinogens, amphetamines and temperature regulation. The Pharmacology of Thermoregulation Symposium, San Francisco, California. 1972. New York: Karger, 1972.

HORITA, A., NAIR, X. and HAMILTON, A.E. L-alpha-methyl-alpha-hydrazino-beta-(3,4-dihydroxyphenyl)propionic acid: Relative lack of antidecarbocylase activity in adrenals. Science 176: 931 (May, 1972)

In rats previously treated with a monoamine oxidase inhibitor, the administration of 5-hydroxytryptophan results in increases in concentrations of 5-hydroxytryptamine in kidney, brain. and adrenal glands. When the peripheral L-aromatic amino acid decarboxylase inhibitor, L-alpha-methyl-alpha-hydrazino-beta-(3,4-dihydroxyphenyl)propionic acid (HMD) is administered prior to 5-hydroxytryptophan, the concentration of 5-hydroxytryptamine in kidneys does not rise, that of the brain increases slightly, and that of the adrenal rises markedly. This indicates that although the adrenal gland is a peripheral organ, it does not respond in the typical manner to the antidecarboxylase action of HMD. These results suggest that HMD does not gain free access into the adrenal medulla and that a possible "blood-adrenal barrier" may exist to this compound.

HOSKO, M.J. and HARDMAN, H.F. Effect of delta-9-THC on cardiovascular responses to stimulation of vasopressor loci in the neuraxis of anesthetized cats. The Pharmacologist 13: 296 (1971)

HOURY, S. and MECHOULAM, R. Benzoxocin and benzoxonin derivatives. Novel groups of terpenophenols with central nervous system activity. Journal of Medicinal Chemistry 17(3): 287-293 (1974)

HUANG, P. and SMITH, A.A. Single dose tolerance to meperidine. Committee on the Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council, 1970.

HUDICK, J.P., WAJDA, I.J. and LAJTHA, A. Isotopic labelling of cholinergic nerve-endings and the effect of drugs. The Pharmacologist 16(2): 541 (1974)

Regional and subcellular studies of choline acetyltransferase of rat brain (Wajda et al., J. Neurochem. 21, 1385, 1973) indicated that this enzyme provides a useful marker for cholinergic nerve-endings and that such organelles from corpus striatum (S) have a higher sedimentation density than those from cerebral cortex (Cx). We have now confirmed these results by specific labelling of cholinergic synaptosomes with H^3- or C^{14}-choline. High affinity choline uptake coincided in S and Cx with the particles characterized as cholinergic synaptosomes, while the low affinity uptake did not have this regional distribution. The specific distribution obtained with high affinity labelling was abolished by hemicholinium-3. The choline uptake systems were further characterized by their kinetic parameters and by their ability to convert accumulated choline to acetylcholine. Morphine treated rats showed slight lowering of Km and Vmax in both S and Cx (P is greater than 0.01). Our data support the idea that high affinity choline uptake labels specifically the cholinergic nerve-endings, and hence is another biochemical marker for these particles.

HUDICK, J.P., WAJDA, I.J. and LAJTHA, A. Regional variations in rat brain synaptosomal transport processes for choline and the effect of morphine. Transactions of the American Society for Neurochemistry, New Orleans, Louisiana, March 10-14, 1974.

Recently it was shown that brain synaptosomes possess both low and high affinity choline uptake systems. Acetylcholine formation and Na^+ dependency were associated exclusively with the' high affinity system. The present report is concerned with regional differences in the low and high affinity choline transports in both normal and morphine treated rats. The three regions studied were: striatum (S), cortex (Cx), and hypothalamus (Hy). Although in all three areas the apparent kinetic parameters for choline uptake increased with higher substrate concentrations, the substrate dependence was more pronounced in Hy than in S and Cx. With high choline concentration (10-100 mu-M), deletion of Na^+ from the incubation medium resulted in a lower Vmax in S and a slightly higher V_{max} in Cx and Hy. The Km was increased by the absence of Na^+ 170% in S, 129% in Cx, and 44% in Hy. The percentage of conversion of accumulated choline to acetylcholine was used as a marker for the high affinity system. With 2 mu-M choline the conversion was 55% in S, 33% in Cx, and 20% in Hy. Absence of Na^+ and presence of 100 mu-M substrate reduced such conversion to less than 10%. Data obtained using rats killed one hour after injection of 30 mg/kg of morphme revealed a small but significant lowering of K_m

Hudick, J.P., Wajda, I. J. and Lajtha, A. Regional variations . . . continued and V_{max} in Cx with 1.0-10.0 mu-M choline. Taking into account the possible variable conditions of different synaptosomal preparations, a conclusive interpretation of this finding awaits further experimentation. The high affinity choline uptake system studied by us is more concentrated in striatum than in the other two parts of the brain. This regional distribution correlates with our earlier report that choline acetyltransferase activity is three fold higher in the striatum. The high affinity transport process appears to reflect a specific accumulation of choline by cholinergic neurons.

HUG, C.C., JR. Characteristics and theories related to acute and chronic tolerance development. Chemical and Biological Aspects of Drug Dependence. Edited by S. Mule and H. Brill. Cleveland, Ohio: Chemical Rubber Company Press, 1972. Pp. 307-358.

HUGHES, J. Isolation of an endogenous compound from the brain with pharmacological properties similar to morphine. Brain Research (in press)

HUGHES, J., KOSTERLITZ, H.W. and LESLIE, F.M. Assessment of the agonist and antagonist activities of narcotic analgesic activities of narcotic analgesic drugs by means of the mouse vas deferens. British Journal of Pharmacology 51: 139-140 (1974)

HUNT, H.F. Unconditioned stimulus functions of drugs: Interpretations, I. Chapter 5 of Stimulus Properties of Drugs. Edited by T. Thompson and R. Pickens. New York: Appleton-Century-Crofts, 1971.

INCIARDI, J.A. and CHAMBERS, C.D. Patterns of pentazocine abuse. Drug Abuse: Current Concepts and Research. Edited by W. Keup. Springfield, Illinois: Charles C. Thomas, 1972.

Pentazocine, an effective analgesic marketed under the trade name Talwin, exerts an euphorogenic effect and, contrary to popular belief, is addictive. The greatest potential for abuse falls within the medical-medicine context; physician overprescription. pharmacists overfilling prescriptions, and inadequate control of institutional drug supplies are common avenues of availability for the narcotic medicine abuser. This ready availability in a legal market and the professional and lay confusion concerning the addiction liability of the drug have contributed to the increasing incidence of abuse and addiction.

ISAAC, W. A study of the relationship between the visual system and the effects of d-amphetamine. Physiology and Behavior 6: 157-159 (1971)

The observed stimulant effect of d-amphetamine as measured by cage activity in the nocturnal animal is at least partially due to the drugs reducing the activity suppressing effect of illumination. The drug had its greatest effect in combination with a lesion of the superior colliculus.

ISAAC, W. and TROELSTRUP, R. Opposite effect of illumination and d-amphetamine upon activity in the squirrel monkey (saimiri) and owl monkey (aotes). Psychopharmacologia 15: 260-264 (1969)

The effect of d-amphetamine upon locomotor activity in the monkey is not uniform and seems related to the noctural-diurnal tendencies of the subject. It increases activity of the nocturnal subject and decreases the activity of the diurnal subject.

ITIL, T. and FINK, M. Electroencephalographic effects of trifluperidol. Diseases of the Nervous System 30: 524-540 (19691

The EEG patterns of trifluperidol, a novel psychoactive agent of the butyrophenone class were determined in acute intravenous and chronic oral administration to psychiatric patients and normal volunteers. The effects were dose related, with increased alpha activity, and increased synchronization occurring at low doses and increased slow wave spike activity and persistence of fast activity at higher dosages.

The EEG patterns are related more to the piperazine phenothiazines than the aliphatic phenothiazine compounds, and the clinical efficacy of these compounds is seen as directly related to the amount and type of central changes induced.

ITIL, T., SHAPIRO, D., HICKMAN, C., FINK, M. and KIREMITCI, N. The differentiation of tranquilizers by quantitative EEG. Electroencephalography and Clinical Neurophysiology 24: 288 (1968)

For abstract, see Section I. Methodology of Drug Research.

ITO, A. and SCHANRERG, S.M. Central nervous system mechanisms responsible for blood pressure elevation induced by p-chlorophenylalanine. The Journal of Pharmacology and Experimental Therapeutics 181(1): 65 (1972)

An elevation in blood pressure was produced in rats after either intracisternal (1-10 mg/kg) or i.p. (100-200 mg/kg) injections of p-chlorophenylalanine. The eievation was dose-related. Pulse and respiration rates showed no significant changes. The pressor response was preceded by selective depletion of serotonin in the brain and was blocked by simultaneous or subsequent treatment with 5-hydroxytryptophan. Data from these and from experiments in which the brain stem was transected sequentially suggest that the pressor response to p-chlorophenylalanine is mediated by depletion of serotonin in the brain stem and that “serotonergic” structures in the rostra1 medulla may exert an important role in central tonic regulation systemic blood pressure in rats.

ITO, A. and SCHANBERG, S.M. Lack of significant central component in beta-adrenergic chronotropic effect in vagotomized rats. Japanese Heart Journal 14(5): 432-439 (September, 19731

The locus of the negative chronotropic response to propranolol was studied in bilaterally vagotomized and respiration-controlled rats. Following results were obtained: 1) The heart rate reduction on intravenous (i.v.) injection of propranolol was most potent for L-, next for DL- and not significant for D-isomer; 2) The response to i.v. DL-propranolol was not affected by the medullo-spinal transection nor by pretreatment with hexamethonium bromide; 3) Intra-cisternal (i.C.) administration of DL-propranolol elicited a dose-relating decrease which was, however, not antagonized by i.C. addition of DL-isoproterenol which caused an increase only inconsistently and not related with dose of the preceding propranolol: and 4) I.C. DL-propranolol did not eliminate the positive chronotropic effect of i.v. injection of DL-isoproterenol. Results indicate a lack of significant central component in the beta-adrenergic negative chronotropic response to i.v. applied propranolol, and suggest the heart rate decrease on the centrally administered propranolol arising in a mechanism other than its beta-adrenergic blocking property.

ITO, A. and SCHANBERG. S.M. Maintenance of tonic vasomotor activity by alpha and beta adrenergic mechanisms in medullary cardiovascular centers. The Journal of Pharmacology and Experimental Therapeutics 189(2): 392 (1974)

A dose-related decrease in blood pressure and heart rate occurred in vagotomized rats after intracisternal (i.c.) injection of phentolamine, an alpha adrenergic antagonist. The site of action of these effects was determined to be localized to the central nervous system. The depressor response was reversed by alpha adrenergic agonist, norepinephrine or phenylephrine, and augmented by the beta adrenergic agonist, isoproterenol. These agonists, however, had no effect on the phentolamine-induced bradycardia. Phenoxybenzamine, an irrever - sible alpha adrenergic antagonist, administered i.c. also caused a decrease in blood pressure and heart rate but these effects were not reversed by norepinephrine. The i.c. injection of norepinephrine without antagonist pretreatment caused a transient increase in blood pressure while isoproterenol caused a decrease. A beta adrenergic antagonist, propranolol, administered i.c. caused a pressor response in small doses and a depressor response in large doses but only a dose-related decrease in heart rate. The propranolol-induced pressor response was reversed by isoproterenol and enhanced by norepinephrine. Data from sequential transections of the brain stem and from direct application of phenylephrine, norepinephrine or isoproterenol on the brain stem surface after transections suggest that the pressor response elicited by alpha adrenergic agonists originates in a region of the medulla localized between the inferior cerebellar peduncle and the caudal end of the obex. The beta adrenergic depressor response, however, appears less localized and to originate from a more diffuse region. These results suggest that alpha adrenergic pressor and beta adrenergic depressor mechanisms are involved reciprocally in tonic blood pressure control mechanisms located in the medulla oblongata of rats. Although the i.c. administration of phentolamine or propranolol also depresses heart rate, the data do not suggest a simple adrenergic mechanism. These studies show clearly that receptor mechanisms for heart rate control in the central nervous system are different from those involved in the regulation of blood pressure.

IWATSUBO, K. and CLOUET, D.H. The effects of narcotic analgesic drugs on the levels and the rates of synthesis of cAMP in six areas of rat brain. Federation Proceedings 32: 536 (1973)

For abstract, see Section II. Drug Chemistry and Metabolism.

IWATSUBO, K., GOLD, G. J. and CLOUET. D. H. Dopamine-sensitive adenylate cyclase of the caudate nucleus of rata treated with morphine or haloperidol. The Pharmacologist 16(2): 270 (1974)

The effects of opiates and neuroleptics on dopamine (DA) sensitive adenylate cyclase (DA-AC) were examined in vitro and in vivo. Various opiate agonists and antagonists at 3 to 300 micromoles had no effect on DA-AC in vitro, while haloperidol in concentrations greater than 3 micromoles completely inhibited the DA response. The administration of morphine or haloperidol in vivo produced significant increases in DA-AC. DA-AC was also increased in rats made tolerant to morphine by pellet implantation. The data are seen to support the hypothesis that while neuroleptics block the DA receptor directly, morphine blocks dopaminergic transmission by some other mechanism, and that the blockade of transmission produces enhanced receptor activity as well as increased DA turnover.

JACOBS, G.R. and BURKS, T.F. Intestinal motor effects of a unique analgesic agent. Journal of Pharmaceutical Sciences 63(5): 787 (May, 1974)

The effects of 2, 3.5, 6,11,11b-hexahydro-11, 11b-dimethyl-14-indolizino (8,7,b)indole hydrochloride on intestinal motility were investigated, The indole derivative altered contractile activity in each preparation studied. Intestinal contractions in situ in anesthetized dogs were stimulated, but variable mild stimulatory or inhibitory effects occurred in cats and monkeys. Spontaneous contractions of monkey intestine were inhibited in vitro. Dose-related increases in motility were produced in dog intestine in vitro, although the experimental compound was considerably less potent than morphine as an intestinal stimulant. The stimulatory effects of the indole derivative in dog intestine were antagonized by atropine and by cyproheptadine. Indolazinoindole also inhibited propulsion of a test meal in mice in vivo.

JACQUET, Y. and LAJTHA, A. A concurrent hyper/hypo-reactive syndrome following morphine microinjection in the midbrain central gray. Journal of Pharmacology 5(Supplement 2): 46 (1974)

Microinjection of morphine into a site in the periaqueductal gray matter (PGM) of the rat resulted in a concurrent hyperlhypo-reactive syndrome not previously observed with systemic injection of morphine. At a moderate dose (5 mu-g), this syndrome was manifested by backward circling in response to auditory/visual stimuli and airpuffs, and simultaneously, moderate analgesia to hemostat pinch to the 4 limbs, tail and ears. At a high dose (10 mu-g), rats showed an explosive hyper-reactivity, making violent and repetitive 2-ft high leaps to auditory/visual stimuli and airpuffs; simultaneously, there was profound hypo-reactivity to noxious pinch, pinpricks and cold stimuli. This hypo-reactivity was such as to allow surgery in a fully conscious rat without signs of pain.

This site is part of the central gray “pain pathway” shown to terminate partly in the posterior hypothalamus (PH). This PH site was shown in a previous study to yield analgesia following morphine microinjection.

JACQUET, Y. and LAJTHA, A. Development of tolerance to morphine following intracerebral injection in the pariaqueductal gray of the rat. Proceedings of the Society for Neuroscience, Fourth Annual Meeting, St. Louis, Missouri, October 20-24, 1974.

Morphine injected via fine-gauge cannula in the rostral periaqueductal gray (PAG) of the rat resulted in profound analgesia accompanied simultaneously by an explosixe hyper-reactivity to sudden auditory and visual stimuli. Both effects were dose-dependent, and could be blocked temporarily by prior intracerebral (IC) naloxone, or reversed temporarily by subsequent IC naloxone. This PAG site showed rapid tolerance development to a toxic dose of morphine. An initial dose of 20 mu-g of morphine bilaterally resulted in a 57% mortality rate, whereas if preceded by I - 3 injections of moderate doses of morphine, the mortality rate was cut to 0. Tolerance was also shown to the analgesic action of IC etorphine (1 mu-g bilaterally) given on 2 successive days. Cross tolerance to the analgesic action of morphine occurred between IC morphine and intraperitoneal (IP) administrations of morphine, as well as between IC morphine and subsequent IP levorphanol. These results indicate that 1) the PAG is a major site of morphine action, and 2) tolerance is a central, and not peripheral phenomenon.

JACQUET, Y.F. and LAJTHA, A. Morphine action at central nervous system sites in rat: Analgesia or hyperalgesia depending on site and dose. Science 182: 490-492 (1973)

Morphine was injected via fine-gauge cannulas permanently implanted in various subcortical sites in the rat brain. In this way the blood-brain barrier was avoided and precise quantities of the drug were delivered to the intended sites. Ten micrograms of morphine in the posterior hypothalamus resulted in significant analgesia, while the same dose injected into the medial septum, the caudate, or the periaqueductal gray matter yielded hyperalgesia. The morphine-produced hyperalgesia at the last-mentioned site was accompanied by stereotyped violent circular leaps, an effect of morphine not previously reported. Thus intra-cerebral injections of morphine differ significantly from systemic injections and produce either analgesia or hyperalgesia. depending on site and dose.

JACQUET, Y. F. and LAJTHA, A. Paradoxical effects after microinjection of morphine in the periaqueductal gray matter in the rat. Science 185: 1055-1057 (1974)

Paradoxical, concurrent hyper- and hyporeactivity of a profound nature to specific stimuli occurred when 10 micrograms of morphine was micro-injected bilaterally into the periaqueductal gray matter of the rat brain. Both effects at this site were dose-dependent. The hyperreactivity (to previously neutral auditory and visual stimuli) was obtained only with intracerbrally injected mor-phine and never with intraperitoneally injected morphine or with other opiates administered either way. Rapid tolerance to toxic doses of morphine developed at this site, as well as cross tolerance of the hyporeactivity to painful stimuli between routes (intraoerebral to intraperitoneal) of morphine administration. Both the hyper- and hyporeactivity were fully reversible by intracerebral injection of naloxone in the periaqueductal gray. Thus, the periaqueductal gray appears to be a major pathway for morphine action.

JAFFE, J., DAHLBERG, C.C., LURIA, J., BRESKIN, S., CHOROSH, J. and LORICK, E. Speech rhythms in patient monologues: The influence of LSD-25 and dextroamphetamine. Biological Psychiatry 4(3): 243-246 (1972)

A comprehensive review of research dealing with drug effects on speech noted a relative paucity of studies in which speech rate was the dependent variable (Waskow, 1967). We have shown that the average durations of sound and silence in 5-min samples of extemporaneous speech are: (i) reliably quantifiable by a completely automated apparatus, (ii) behaviorally stable parameters of individual speakers; and (iii) systematically modifiable when subject, task, and environmental variables are manipulated (Jaffe and Feldstein. 1970; Jaffe and Breskin, 1970a. 1970b). We now assess the effects of LSD and dextroamphetamine (DA) on these temporal characteristics of speech.

JAFFE, J., DAHLBERG, C.C., LURIA, J. and CHOROSH, J. Effects of LSD-25 and dextroamphetamine on speech rhythms in psychotherapy dialogues. Biological Psychiatry 6(1): 93-96 (1973)

We have previously reported the effects of LSD-25 and dextroamphetamine (DA) on the sound-silence pattern of extemporaneous monologues (Jaffe et al., 1972). A monologue consists of a sequence of vocalizations interrupted by pauses. The major finding was that, with respect to placebo (P), the average pause duration was lengthened by LSD and shortened by DA, whereas mean vocalization duration was not affected significantly. This modification of pause duration is one major mechanism by means of which speech rate is controlled. The monologues were recorded in isolation, and immediately prior to psychotherapy dialogues in a double-blind study of the drug effects on the treatment process. It is thus reasonable to ask if the effects of the drugs on the dialogues are the same as those occurring in the monologues; the answer is in the affirmative.

JANDHYALA, B.S., MALLOY, K.P. and BUCKLEY, J.P. Effects of delta-g-tetrahydrocannabinol (delta-9-THC) on pulmonary circulation. Federation Proceedings 34(3): 744 (1975)

It has been reported that delta-9-THC accumulated in large concentrations in lung tissue and can produce hypoxic hypoxia in spontaneously breathing animals. The present study was designed to investigate the effects of delta-9-THC, on pulmonary circulation and possible consequences on right ventricular performance in anesthetized mongrel dogs. Delta-9-THC (2.5 mg/kg i. v.) produced a decrease in heart rate (HR), pulmonary blood flow (PBF) and transient changes in right ventricular stroke volume (RVSV). The decrease in PBF was not accompanied by a reduction in pulmonary artery pressure evidently due to a marked increase in pulmonary vascular resistance (PVR). Increased PVR could also account for gradual and consistent increases in right ventricular stroke work (RVSW) despite reduced PBF. When changes in HR were prevented by a pacemaker there was still a significant reduction in PBF accompanied by a marked increase in PVR. However, in the preparations in which HR was constant there was a reduction in RVSV. RVSW also decreased despite a marked increase in PVR. These changes could only be explained on the basis of decreased venous return following delta-9-THC. Results of this investigation are consistent with the conclusion, that in subjects with normal cardiac rhythm, delta-9-THC could enhance RVSW (pressure-work) due to marked increase in pulmonary vascular resistance.

JESPERSEN, S. and SCHEEL-KRÜGER, J. Antagonism by methysergide of the 5-hydroxytryptamine-like action of toxic doses of fenfluramine in dogs. Journal of Pharmacy and Pharmacology 22: 637-638 (1970)

In summary a large dose of fenfluramine given to dogs caused symptoms which were grossly similar to those reported after administration of 5-HTP, indicating that 5-HT plays an important role in the reactions. The symptoms improved after administration of the 5-HT antagonist methysergide, which also seemed to antagonize the fenfluramine-induced anorexia.

Methysergide might be of value in the treatment of fenfluramine overdosage.

JESPERSEN, S. and SCHEEL-KRÜGER, J. Evidence for a difference in mechanism of action between fenfluarmine- and amphetamine-induced anorexia. Journal of Pharmacy and Pharmacology 25: 49-54 (1973)

The influence of drugs, active on 5-hydroxytryptamine (5-HT) mechanisms, has been examined on the anorexigenic activity of fenfluramine and (+)-amphetamine in rats trained to consume their daily food ration during 6 h. Chlorimipramine, which inhibits the re-uptake mechanisms in central 5-HT neurons, and the 5-HT blocking drugs methergoline and methysergide were used. Fenfluramine, 7.5 mg kg^{-1}, and amphetamine, 2.5 mg kg^{-1}, given $\frac{1}{2}$ h before feeding reduced the food intake during the following 2 h to approximately 40% compared with control days. Pretreatment with metherpoline in the optimal dose (1 mg kg^{-1}) produced only a weak but significant antagonism to amphetamine anorexia, whereas the fenfluramine anorexia was strongly antagonized by methergoline in all doses tested (0.3, 1 and 3 mg kg^{-1}). Methysergide (0.1, 0.3, 1 and 3 mg kg^{-1}) showed no significant antagonism against amphetamine or fenfluramine anorexia. Chlorimipramine produced a strong antagonistic effect to the fenfluramine anorexia, but showed no antagonism against amphetamine. In contrast the highest dose of chlorimipramine (20 mg kg^{-1}) potentiated amphetamine anorexia. The present results together with other evidence discussed support the conclusion that 5-HT mechanisms are involved in fenfluramine anorexia, whereas amphetamine anorexia seems mainly correlated with catecholamine dependent mechanisms.

JOHNSON, C.L. and GREEN, J.P. Molecular orbital studies on tryptamines active on the LSD receptor of the rat fundus strip. International Journal of Quantum Chemistry: Quantum Biology Symposium 1: 159-167 (1974)

JOHNSON, J.C. and CLOUET, D.H. Studies on the effect of acute and chronic morphine treatment on catecholamine levels and turnover in discrete brain areas of rats. Federation Proceedings 32: 757 (1973)

For abstract, see Section II. Drug Chemistry and Metabolism.

JONAS, W. and SCHEEL-KRÜGER, J. Amphetamine induced stereotyped behavior correlated with the accumulation of 0-methylated dopamine. Archives internationales de Pharmacodynamie et de Therapie 177: 379-389 (1969)

For abstract, see Section II. Drug Chemistry and Metabolism.

JONAS, W. and SCHEEL-KRÜGER, J. Pharmacological studies on tetrabenazine induced excited behaviour of rats pretreated with amphetamine or nialamide. Archives internationales de Pharmacodynamie et de Therapie 206: 47-65 (1973)

Tetrabenazine (50 mg/kg) injected 1½ h after various doses of amphetamine (0.25-10 mg/kg) produced a 5-10 times potentiation of the amphetamine-induced gross behavioural effects in rats: locomotion, rearing and stereotyped activities. However, the amphetamine-tetrabenazine excitation was shortlasting, 6-36 min dependent on the amphetamine dose. Tetrabenazine (50 mg/kg) injected after cessation of the amphetamine excitation (i.e. 4½ h after 5 mg/kg amphetamine) was also able to reinduce a shortlasting and typical amphetamine-like stimulation lasting 12-18 min. Neuroteptic drugs with dopamine receptor blocking properties haloperidol, perphenazine and spit-amide produced in very small doses complete inhibition of all behavioural effects in the amphetamine-tetrabenazine reversal test, whereas noradrenaline receptor blocking drugs aceperone and phenoxybenzamine in very high doses only produced partial inhibition of the locomotor and rearing activities. Scopolamine increased the tetrabenazine reversal effect. A single, relatively low, dose of alpha-methyltyrosine (100 mg/kg) produced no inhibition of the amphetamine-tetrabenazine excitation, whereas high repeated doses of alpha-methyltyrosine (2X350 mg/kg) or reserpine (7.5 mg/kg) produced complete inhibition of the amphetamine-tetrabenazine excitation. The present studies indicate that the strong potentiation effect of tetrabenazine in amphetamine pretreated rats is dependent on a tetrabknazine-induced release of the catecholamines from a reserpine sensitive storage pool to an extragranular pool available for amphetamine release. The excitation produced by nialamide-tetrabenazine was found very longlasting but not as strong and intense in appearance as after amphetamine. The nialamide-tetrabenazine excitation was potentiated by scopolamine, completely antagonized by the dopamine antagonist spiramide and partially antagonized by the noradrenaline antagonists, aceperone and phenoxybenzamine.

JONES, R. Significance and characteristics of drug dependence: Characteristics of drug dependence to cannabis. Chemical and Biological Aspects of Drug Dependence. Edited by S. J. Mule and H. Brill. Cleveland, Ohio: Chemical Rubber Company Press. 1972. Pp. 65-81.

JONES, R.T. and STONE, G.C. Psychological studies of marijuana and alcohol in man. Psychopharmacologia 18(1): 108-117 (1970)

Regular users of marijuana (cannabis sativa) were given smoked and orally administered marijuana, a placebo, or alcohol. They were unable to distinguish between smoked marijuana and the tetrahydrocannabinol-free placebo. The oral administration of tincture of cannabis produced primarily dysphoric symptoms and was similar to alcohol in this respect. The smoked marijuana altered pulse rate, time estimation, and EEG, but had no effect on a measure of field dependent or on a digit symbol substitution task. Both drugs appeared to be mild intoxicant in a laboratory setting. Consideration of the dose, prior experience with drugs, setting, and possible cross tolerance of marijuana and alcohol are important in evaluating the significance of the clinical effects.

KALLMAN, M.W. and ISAAC, W. The effects of age and illumination on the dose-response curves for three stimulants. Psychopharmacologia (in press)

KANG, S. and GREEN, J.P. Correlation between activity and electronic states of hallucinogenic amphetamines. Nature 226(5246): 645 (May 16, 1970)

KANG, S. and GREEN, J.P. Steric and electronic relationships among some hallucinogenic compounds. Proceedings of the National Academy of Sciences 67(1): 62-67 (September, 1970)

For abstract, see Section II. Drug Chemistry and Metabolism.

KANG, S., SESSA, G. and GREEN, J.P. Spectroscopic observations of synaptosomal membranes: The effect of morphine. Research Communications in Chemical Pathology and Pharmacology 5(2): 359 (March, 1973)

KARLER, R., CELY, W. and TURKANIS, S.A. The anticonvulsant activity of cannabidiol and cannabinol. Life Sciences 13: 1527 (1973)

The anticonvulsant activity of delta-9-tetrahydrocannabinol was compared with that of two other naturally occurring cannabinoids. cannabidiol and cannabinol, in a maximal electroshock test in mice. The drugs were administered as an emulsion of sesame seed oil, Tween 80 and saline to mice i.p. The results indicate that all three cannabinoids are effective anticonvulsants. The time for peak effect is about 2 hr. In terms of relative potencies, cannabidiol and delta-9-THC are similar but both of them are more active than cannabinol.

KARLER, R., CELY, W. and TURKANIS. S.A. Anticonvulsant activity of delta-9-tetrahydrocannabinol and its 11-hydroxy and 8-alpha, 11-dihydroxy metabolites in the frog. Research Communications in Chemical Pathology and Pharmacology 9(3): 441-452 (November, 1974)

For abstract, see Section II. Drug Chemistry and Metabolism.

KARLER, R. CELY, W. and TURKANIS. S.A. Anticonvulsant properties of delta-9-tetrahydrocannabinol and other cannabinoids. Life Sciences 15: 931 (1974)

Anticonvulsant doses of delta-9-tetrahydrocannabinol (delta-9-THC) markedly lower body temperature in mice at an ambient temperature of 22° C, but there is little such effect at 30° C. The anticonvulsant properties of delta-9-THC are as follows: The drug abolishes hind-limb extension in a maximal electroshock (MES) test, elevates both the MES (extensor) and 6-Hz-electroshock thresholds, exerts no effect on the 60-Hz-electroshock threshold, and enhances minimal seizures caused by pentylenetetrazol. All anticonvulsant properties studied, with the exception of the 60-Hz-electroshock threshold, were unaffected by the hypothermia resulting at 22° C. Additional experiments with delta-9-THC indicated that chronic treatment results in the development of tolerance, as determined by the MES test with rats. The four principal naturally occurring cannabinoids, delta-9-THC, delta-8-THC, cannabinol and cannabidiol, display anticonvulsant activity, as does the major, primary metabolite of delta-9-THC, 11-hydroxy-delta-9-THC. Of all agents investigated in mice, the synthetic cannabinoids, dimethylheptylpyran and its isomers, are the most potent anticonvulsants. The results of a study of the relative motor toxicity and anticonvulsant activity of the cannabinoids demonstrate that these properties are at least partially separable among the various agents.

KARLER, R., CELY, W. and TURKANIS, S.A. A study of the development of tolerance to an anticonvulsant effect of delta-9-tetrahydrocannabinol and cannabidiol. Research Communications in Chemical Pathology and Pharmacology 9(1): 23 (September, 1974)

Tolerance to delta-9-tetrahydrocannabinol, cannabidiol, diphenylhydantoin and phenobarbital was studied with a maximal. electroshock test in mice. Tolerance to all four drugs developed very rapidly. Hexobarbital sleep times of animals tolerant to delta-9-tetrahydrocannabinol and phenobarbital were unchanged; whereas cannabidiol tolerance was accompanied by an increase, and diphenylhydantoin tolerance by a decrease in sleep time. In addition, cross-tolerance between the two cannabinoids and diphenylhydantoin and phenobarbital was demonstrable. These results suggest that the mechanism of tolerance to the cannabinoids' nticonvulsant effect in mice is probably dependent upon an adaptation of the central nervous system.

KARLER, R., CELY, W. and TURKANIS. S.A. A study of the relative anticonvulsant and toxic activities of delta-9-tetrahydrocannabinol and its cogeners. Research Communications in Chemical Pathology and Pharmacology 7(2): 353 (February, 1974)

The relative anticonvulsant and toxic activities of delta-9-tetrahydrocannabinol were compared with those of cannabidiol and dimethylheptylpyran. Anticonvulsant activity was determined in a maximal electroshock test and toxicity in a bar-walk test. The data were expressed in terms of protective indices (TD50/ED50). The results indicate that the anticonvulsant and toxic properties of these cannabinoide are separable. The order of relative toxicity was dimethylheptylpyran greater than delta-9-tetrahydrecannabinol greater than cannabidiol.

KAUFMAN, J.J. Quantum chemical and theoretical techniques for the understanding of psychoactive drugs and narcotic agents. Proceedings of the International Conference on Computers in Chemical Research and Education. Ljublajana, Yugoslavia (in press)

KAUFMAN, J.J. and KERMAN. E. Quantum-chemical and theoretical techniques for the understanding of the action of drugs which affect the central nervous system. Jerusalem Symposia on Quantum Chemistry and Biochemistry 6: 524-547 (1974)

A method (sensitivity 1-2 ng/ml) for the estimation of methadone-^{3}H (sp. act. 5 mu-Ci/ma) from biological materials provided recoveries of 95-99%. Following a 10 mg/kg s.c. injection to male Wistar rats, peak plasma levels of 1.1-1.2 mu-g/ml were obtained at 30 min. to 1 hr. The levels declined to 10 ng/ml at 24 hr. and were barely detectable at 48 hr. Peak brain conc. at 30 min. to 1 hr. ranged between 3.8-4.5 mu-g/g. Extensive localization of drug and metabolites occurred in lung (66.7 mu-g/g), duodenum (34.2 mu-g/g). kidney (19.7 mu-g/g), liver (18.6 mu-g/g) and heart (11.7 mu-g/g) hr. after injection. Extractable radioactivity was detected in brain and other tissues 3 weeks after injection. Excretion of methadone and metabolites in urine and feces was slow, and prolonged with approx. 25-30% of the dose accounted for in 48 hr. The distribution profile after oral administration (10 mg/kg) was qualitatively similar to that after s.c. injection, however, peak plasma and brain levels were approx. 1/10 and 1/25 of those obtained after s.c. administration, respectively. Methadone and metabolites persisted in the duodenum and other tissues 'for more than 1 week. Besides 2-ethylidene-1,5-dimethyl-3.3-diphenyl pyrrolidine, evidence for the formation of 1 nonconjugated and 3 glucuronide conjugated urinary metabolites was obtained on column and thin layer chromatography.

KAUFMAN, J.J., KERMAN. E. and KOSKI, W.S. Quantum chemical, other theoretical and physicochemical studies on narcotics and narcotic antagonists to understand their mechanism of action. International Journal of Quantum Chemistry - Symposia Issue 1: 289 (1974)

The topological and topographical requisites for effective narcotic and narcotic antagonist action are outlined. Quantum chemical calculations by several methods have been carried out for these drugs. CNDO/2 and PCILO results are compared for morphine and nalorphine, both for the free bases and the protonated forms. CNDO/2 results are presented for some additional narcotics and narcotic antagonists: naloxone, cyclazocine and methadone. The CNDO/2 calculated electron densities on the nitrogens are very close in the free bases of the N-methyl and the N-ally1 congeners and they are also very close in the protonated forms of these compounds, contrary to the assumption usually held by chemists that the electron density on the nitrogen is lower in the allyl compound which is what makes it a weaker base. Also, as we first showed many years ago for pyridine aldoximes the positive charge in the N-protonated species is not localized on the nitrogen but spread over many of the neighboring atoms. Both of the above results on the charge distributions on the nitrogens were experimentally given credence by the ESCA results of Carlson and Saethre.

KAUFMAN, J.J. and KOSKI, W.S. Physicochemical, quantum chemical and other theoretical techniques for the understanding of the mechanism of action of CNS agents: Psychoactive drugs, narcotics and narcotic antagonists and anesthestics. Drug Design, Vol. V. Edited by E. J. Ariens. New York: Academic Press, 1971.

KAUFMAN, J.J., SEMO, N.M. and KOSKI, W.S. Microelectrometric titration measurement of the pK_a's, partition and drug distribution coefficients of narcotics and narcotic antagonists and their pH and temperature dependence. Journal of Medicinal Chemistry (in press)

The pK_a's, partition coefficients and drug distribution coefficients (apparent partition coefficients) have been investigated for a number of narcotics and where possible for their congener narcotic antagonists. These studies were carried out by a microelectrometric titration technique as a function of temperature and pH. This method enables one to determine not only the dissociation constants to deconvolute overlapping pK_a's, but also to determine the solubilities and oil-water distribution of these various drugs.

KAYMAKCALAN, S. and DENEAU, C.A. Some pharmacological effects of synthetic delta-9-THC. The Pharmacologist 13(2): 247 (1971)

THC produced analgesia in Sprague Dawley rats (ED_{50} 10.1 mg/kg s.c.) as determined by the hot-plate technique. A single s.c., dose of 10 mg/kg produced tolerance which persisted for more than 1 month. The analgesic effect of a combination of THC and morphine in rats was greater than additive. In cats, vocalizations resulting from i.p. injections of phenylquinone or acetic acid were reduced 65-85% with 1 mg/kg THC s.c. 1 mg/kg THC s.c. reduced the motor activity of cats but enhanced the excitatory effect of morphine. SKF 525A increased (not statistically significant) the analgesic effect of THC in rats and hepatectomized rats showed a significantly greater effect than sham-operated controls indicating that THC itself, and not a metabolite is, the active drug. A single dose of 10 mg/kg THC s.c. reduced I^{125} uptake by the rat thyroid by 27% at 4 hours but repeated doses of THC (10 mg/kg qbh) did not affect 24-hour I^{125} uptake. THC produced hypothermia in rats, cats, dogs and monkeys and bradycardia in cats. dogs and monkeys.

KELLY, R.J. and BURKS, T.F. Relative vasoconstrictor potencies of norepinephrine, alpha-methylnorepinephrine and octopamine. Archives internationales de Pharmacodynamie et de Therapie 208(2): 306 (April. 1974)

Blood pressure responses to l-norepinephrine, l-alpha-methylnorepinephrine and dl-octopamine were measured in anesthetized dogs. Alpha-methylnorepinephrine was 0.3 as potent as norepinephrine in raising blood pressure, octopamine was 0.02 as potent. These potency ratios applied under control conditions, after cholinergic blockade and after beta adrenergic blockade. Vasoconstrictor responses were measured in dog isolated mesenteric arteries. Again, alpha-methylnorepinephrine was 0.3 as potent as norepinephrine, octopamine was only 0.002 as potent as norepinephrine. Both alpha-methylnorepinephrine and octapamine responses were antagonized by phentolamine and enhanced by cocaine. The slight difference in potency between alpha-methylnorepinephrine and norepinephrine may be insufficient to explain completely the hypotensive properties of alpha-methyldopa. Octopamine could, however, serve as a false adrenergic neuro-transmitter substance.

KENNEDY, D.K., GRUBB, M.N. and BURKS, T.F. Antagonism of methadone's intestinal effects by cyproheptadine. Gastroenterology 66: 396-402 (1974)

The narcotic agonist methadone increases the amplitude of intestinal phasic contractions and can retard intestinal propulsive activity. Like morphine, methadone may produce its intestinal effects by release of local 5-hydroxytryptamine (5-HT). The ability of the 5-HT receptor blocking agent cyproheptadine to antagonize the intestinal effects of methadone was evaluated in vitro and in vivo. In vascularly perfused segments of dog isolated intestine, cyproheptadine decreased the stimulatory effect of methadone and 5-HT, but not the effect produced by bethanechol, a cholinergic agonist. Atropine decreased responses to methadone, 5-HT, and bethanechol because one component of 5-HT action is mediated by intramural cholinergic nerves. Cyproheptadine also antagonized the methadone-induced reduction in transit of test meals in mice. The LD_{50} of methadone was not altered by cyproheptadine. The ability of a 5-HT blocking agent to antagonize the intestinal effects of methadone suggests a potentially useful means of overcoming one of the troublesome side effects of the narcotic drugs;

KERR, F. W. Morphine self-administration in dependent monkeys: Reduction by hypothalamic lesions. IRCS International Research Communications System (73-12) 7-1-6

KERR, F.W. The role of the lateral hypothalamus in morphine dependence. Narcotics and the Hypothalamus. Edited by E. Zimmermann and R. George. New York: Raven Press, 1974. Pp. 23-24.

KERR, F.W. Tolerance to morphine and the bloodbrain-CFS barrier. Federation Proceedings 33: 528 (1974)

Tolerance to the CNS effects of morphine and other opiates has never been satisfactorily explained. In this study adult Sprague Dawley rats were used. The lethal dose of morphine by intraventricular injection in naive rats was established to be 1 mg. (L.D. 50 was approximately 0. 5 mg while 0.25 mg was compatible with survival) 24 rats were made tolerant to increasing doses of morphine till at 1 month they were receiving 100 mg twice daily intraperitoneally. Ventricular cannulae were then placed stereotaxically into the left lateral cerebral ventricle and secured with acrylic. 24 hours later they received either 1 mg or 2 mg of morphine intraventricularly. These doses of drug were lethal in all cases in which the injection entered the ventricular system. Pantopaque ventriculography was done in every instance to confirm correct placement.

These results suggest that tolerance is due to increasing effectiveness of the blood brain barrier rather than to changes occurring in the neurons themselves.

KERR, F.W. and POZUELO, J. Suppression of physical dependence and induction of hypersensitivity to morphine by stereotaxic hypothalamic lesions in addicted rats and a new theory of addiction. Drug Addiction: Experimental Pharmacology Vol. 1. Edited by J. M. Singh, L. H. Miller and H. Lal. Mount Kisco, New York: Futura Publishing Company, 1972.

The basic mechanisms underlying opiate tolerance and addiction have not as yet been elucidated despite intensive efforts by numerous investigators employing a wide variety of behavioral, biochemical and immunological techniques. many of which have been reviewed recently.

The role of the central nervous system in narcotic addiction is paramount, and it is generally believed that dependence is a result of widespread involvement of cortical and subcortical centers. The alternative possibility, that opiates might exert their addictive effects on quite limited nuclear areas of the CNS, is the subject of this investigation.

The hypothesis to be tested was that narcotic addiction might be an expression of disordered function of centers which control intake of solids or liquids and thus comparable to a pathological type of hunger or thirst. Since the centers which regulate these functions are located in the hypothalamus the hypothesis could be subjected to experimental investigation along the lines to be described.

An extensive review of the literature has failed to reveal any previous report of suppression of physical dependence on opiates: a preliminary report on this work has been made.

KERR, F.W., TRIPLETT, J.N., JR., and BEELER, G.W. Reciprocal (push-pull) effects of morphine on single units in the ventromedian and lateral hypothalamus and influences on other nuclei: With a comment on methadone effects during withdrawal from morphine. Brain Research 74: 81-103 (1974)

The effects of morphine and of its antagonists naloxone and nalorphine on multiple single units recorded simultaneously in the ventromedian nucleus (VMN) and in the lateral hypothalamic area (LHA) and certain other neuronal groups were investigated in naive and morphine dependent adult Sprague-Dawley rats using pulse height analysis techniques and computer generated firing frequency histograms.

Morphine produced diametrically opposite effects on VMN and LHA in both naive and dependent animals: with the exception of a few units, neurons recorded from the VMN were excited by morphine and. conversely, those in LHA were inhibited; the antagonists naloxone and nalorphine produced clear-cut reversal of these effects. During withdrawal phases in addicted animals, firing rates in the LHA were greater than rates recorded in the same area of naive animals; no significant differences between firing rates in the VMN of naive and addicted animals were observed.

Methadone effects were investigated in morphine dependent rats in withdrawal; both VMN and LHA neurons were excited by methadone and the effect of morphine on these nuclei was reversed.

The possible implications of these observations for localization of mechanisms in opiate dependency and for the concept of methadone blockade are discussed.

KHALSA, J.H. and DAVIS, W.M. Effects of chronic alpha-methyltyrosine on the locomotor activity response to morphine and amphetamine in rats. The Pharmacologist 15(2): 219 (1973)

Two groups (36 each) of male Wistar rats weighing ca. 230 g. were treated ip with either L-alpha-methyl-p-tyrosine (AMT; 50 mg/kg. suspended in saline) or saline (SAL) twice daily for 15 or 18 days. Rats from each group were treated with either SAL, morphine sulfate (MS; 5 mg/kg, ip), or d-amphetamine sulfate (AS; 1 mg/kg, ip) 4 h after the a.m. dose of AMT on days 1, 3, 6, 9, 12, 15 and 18 of AMT treatment and at 28, 52 or 96 h after the last AMT dose. Locomotor activity was recorded for 2 h immediately after SAL, MS or AS. Tolerance developed to the blocking action of AMT on MS-induced hypermotility within the first 6 days. Such tolerance was not seen toward the AMT antagonism of AS-induced hypermotility. After AMT was discontinued, motility was significantly higher in AMT-MS rats than in SAL-MS rats following a single further dose of MS, suggesting an induction of CNS supersensitivity to the stimulatory action of MS. However, such supersensitivity to the action of AS following withdrawal of AMT, as reported by Beuthin et al. (J. Pharmacol. exp. Ther. 181: 446, 1972) for rats receiving chronic oral AMT, was not observed by us.

KHALSA, J.H. and DAVIS, W.M. Inhibition of motility response to morphine or d-amphetamine and of feeding behavior in rats by U-14,624. Federation Proceedings 33: 564 (1974)

We have extended our previously reported study with chronic alpha-methyltyrosine, a tyrosine hydroxylase inhibitor by using a dopamine-beta-hydroxylase inhibitor, U-14,624 (U), 1-phenyl-3-(2-thiazolyl)-2-thiourea. Chronic treatment of two groups of rats (36 each) with U (25 mg/kg ip once daily) prevented the hypermotility induced in rats by morphine sulfate (MS; 5 mg/kg, ip) when tested at 6 hrs. after U on days 1, 3, 6, 9, 12, 15, or 18. Tolerance developed to the blocking effect of U on hypermotility induced by d-amphetamine sulfate (AS: 1 mg/kg. ip) within 9 days. Such tolerance was not seen towards the U-antagonism of MS-induced hyperactivity. Withdrawal from chronic U treatment produced no supersensitivity to the CNS stimulant actions of either MS or AS at 30, 56, 78 or 102 hrs. after the last dose of U. Single ip or po doses of U (25 mg/kg) did not inhibit feeding behavior or spontaneous locomotor activity. However, doses of 50 or 75 mg/kg either ip or po, which inhibited locomotor activity also reduced food intake significantly for 3 days after a single treatment.

KHAZAN, N. Declining levels of electrocorticogenesis and their response to morphine in the morphine dependent rat. Federation Proceedings 29(2): 781 (1970)

In pursuing earlier studies on EEG-EMG correlations of behavior during morphine addiction in the rat (Khazan, et al., J. Pharmacol. Exp. Therap., 155: 521, 1967), electrocorticogenesis. the integrated or mean voltage output of the electrocorticogram, was investigated along with longitudinal EEG-EMG tracings. Morphine sulphate, 1.25 mg/kg. was automatically injected, i.v., every hour for 24 hours. The dose was increased each succeeding day to 2.5, 5, 10 and 20 mg/kg per hour respectively. This preparation induced a state of morphine dependence in these rats. It was found that an almost immediate and progressive increase of the levels of electrocorticogenesis followed morphine injections, accompanied by a marked decrease in viciousness and irritability of the rat. When morphine injections were discontinued, a progressive fall in the EEG electrogenesis occurred which was then followed by arousal, irritability and "wet dog" withdrawal symptoms. It is assumed that along with the development of "behavioral" tolerance and physical dependence to morphine, an "EEG": suppressant mechanism develops to counteract the acute EEG -deactivation effects of morphine and which then dominates in the morphine dependent rat. Thus, with a quantitative approach to the study of the longitudinal EEG output, the existence of low levels of electrocorticogenesis in the morphine dependent rat following morphine withdrawal was revealed.

KHAZAN. N. EEG correlates of morphine dependence and withdrawal in the rat. Drug Addiction: Experimental Pharmacology Vol. 1. Edited by J.M. Singh, L.H. Miller and H. Lal. Mount Kisco, New York: Futura Publishing Company, Inc. 1972. Pp. 159-172.

For abstract, see Section I. Methodology of Drug Research.

KHAZAN, N. EEG-EMG studies of morphine-like narcotics and antagonists. Journal de Pharmacologic 5(Supplement): 506 (1974)

Adult female rats were implanted with chronic electrodes to record the cortical EEG and the temporalis muscle EMG, as well as with i.v. cannulas for drug administration. The induction of EEG slow bursts by morphine, methadone and l-alpha-acetyl-methadol. and also by the morphine antagonist, nalorphine. was demonstrated. In contrast, the "pure" morphine antagonists, naloxone and naltrexone, which blocked morphine's EEG and behavioral effects, failed to induce these same changes when given alone. The longitudinal monitoring of EEG-EMG and sleep-awake activity of the control. dependent. and abstinent rat enabled thorough characterization of tolerance and physical dependence. the drug-seeking behavior, and immediate and protracted abstinence. The study of the EEG and behavioral correlates of acute and long-term effects of morphine and methadone provided further support for analogous states of dependence and abstinence produced by these narcotics. This animal model should be helpful in the evaluation of the efficacy and duration of action of narcotic antagonists in blocking relapse in the post-addict rats self-administering morphine.

KHAZAN, N. Electrophysiological correlates of the action of drugs in the brain. Introduction to Psychopharmacology. Edited by R.H. Rich and K.E. Moore. New York: Raven Press, 1971.

KHAZAN, N. Longitudinal EEG study of the effects of morphine injections and withdrawal in the morphine dependent rat. Committee on the Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council, 1970.

We previously reported on electroencephalographic (EEG). electromyographic (EMG), and behavioral correlates of the rat during cycles of dependence to morphine, self-injected on a fixed ratio schedule. EEG "slow bursts" of four to seven Hz were noted during the development of morphine tolerance and physical dependence, when rats received hourly injection of the drug. The animals then learned to bar press for morphine self-injection. Inter-injection intervals lasted about two to, three hours at FR 20 schedule. During this stage of self-maintained addiction, the EEG "slow bursts" appeared immediately after morphine injection, becoming more frequent within 20 to 30 minutes and disappearing before the following injection. Furthermore, the longitudinal EEG-EMG collected elicited prolonged episodes of sleep interrupted by frequent and unusually long rapid-eye-movement (REM) sleep which predominated prior to morphine self-injection, followed by wakefulness thereafter, and upon withdrawal, no EEG "slow bursts" appeared.

Recently, we constructed a modified experimental set-up whereby EEG-EMG tracings. from five freely moving rats with chronically implanted electrodes and iv cannulae. could be collected simultaneously and analyzed for the EEG-frequency and energy content. We have undertaken the present investigation in an attempt to expand our earlier findings on the EEG-EMG and behavioral aspects of morphine dependence and withdrawal in the rat.

KHAZAN, N. and BROWN, P. Differential effects of three tricyclic antidepressants on sleep and REM sleep in the rat. Life Sciences 9(Part I): 279-284 (1970)

The closely related dibenzazepine antidepressants desipramine (Pertofran), imipramine (Tofranil) and trimipramine (Surmontil), have been reported to possess different drug profiles while retaining their antidepressant property. Desipramine shows the highest degree of psychomotor activation with almost no sedative anti-anxiety component, whereas trimipramine has the richest anxiety reducing property with no psychomotor activation. Both of these properties are moderately displayed by imipramine. In addition, trimipramine shows no anti-reserpine effect, while this activity is easily demonstrated by both imipramine and desipramine.

The differences in the pharmacociynamic and clinical drug profiles of the above antidepressants, and the currently disputed role of Rapid Eye Movement (REM) sleep in depression, prompted the present comparative study of their effects on REM sleep.

KHAZAN, N. and BROWN, P. REM sleep blocking effects of imipramine and trimipramine in the rat. The Pharmacologist 11: 780 (1969)

Imipramine (Tofranil) and trimipramine (Surmontil) are closely related dibenzazepines. Unlike imipramine, trimipramine was shown to be ineffective in reversing the reserpine syndrome and, clinically was described as an antidepressant with psychomotor sedative "anxiolytic" component. This study was carried out in an attempt to investigate further the REM sleep suppressant properties of psychotropic drugs. Rats with chronic cortical and neck muscle electrodes were used. EEG-EMG tracings were collected from the freely moving rats for a period of 5 to 10 hours. Imipramine and trimipramine were given i.p. in doses of 5. 10 and 20 mg/kg. Saline treated rat showed an average of 1.5 to 2 REM sleep episodes per hour. Imipramine treatment resulted in a significant suppression of REM sleep episodes while sleep-awake alternation was left intact. On the other hand, trimipramine showed no blocking effect on REM sleep even at the highest dose. Thus, imipramine which has been shown to have relatively high anti-reserpine activity and weak anti-anxiety activity, suppresses REM sleep, whereas, trimipramine, which has low anti-reeerpine activity and high anti-anxiety activity, does not suppress REM sleep.

KHAZAN, N. and COLASANTI, B. Decline in the mean integrated electroencephalogram voltage during morphine abstinence in the rat. The Journal of Pharmacology and Experimental Therapeutics 177(3): 491 (1971)

Direct, voltage-integrated and frequency-analyzed cortical electro-encephalograms (EEG's) as well as integrated electromyograms were obtained from control, morphine-dependent and abstinent rats prepared with chronically implanted cortical electrodes and i.v. cannulas. Morphine sulfate, 1.25 mg/kg was injected automatically every hour for 24 hours during the first day. This dose was increased on successive days to 2.5, 5, 10 and 20 mg/kg/hr. resulting in the induction of a state of morphine dependence in the rats. When morphine injections were discontinued, the behavioral manifestations of the abstinence syndrome became evident. During this period, a decline in the mean integrated EEG voltage prevailed throughout the sleep-awake cycle. This drop of the EEG voltage output reached levels 35 to 70% below those of control. The lowered

Khazan, N. and Colasanti, B. Decline in the mean . . . continued

voltage output of the awake state EEG endured for two to three days. The reduction of the EEG voltage output of the sleep' state, however, was more pronounced and longer lasting, with recovery reached by the fourth or fifth day of abstinence. Morphine injections given during the abstinence syndrome produced an immediate rise in the low voltage output: this rise was accompanied by a marked decrease in the irritability and arousal of the abstinent rat. It is suggested that the lowered voltage output of the EEG during morphine abstinence is the product of a central nervous system mechanism developed to counteract the acute effects of morphine as to synchronization of the EEG.

KHAZAN, N. and COLASANTI, B. Differential pharmacodynamics of morphine injection in naive and postaddict rats; EEG correlates. Federation Proceedings 30: 277 (1971)

High voltage EEG slow bursts have been reported to follow morphine administration in experimental animals and in man. The present study has been undertaken to explore the possible existence of "long-term" morphine effects in post-addict rats in comparison with naive rats in EEG terms. Adult female Sprague-Dawley rats prepared with chronically implanted cortical and temporal muscle electrodes and i.v. cannulae were used. Morphine injections of 10 mg/ kg were given i.p. to naive rats and to post-addict rats at successive intervals following morphine withdrawal. These intervals extended in a few cases up to one year. In the naive rat, high voltage EEG slow bursts associated with stuporous behavior appeared almost immediately after injection and prevailed for 60 to 90 minutes. This phase was followed by continuous EEG and behavioral arousal for another period of 60 to 90 minutes, after which sleep appeared. In contrast, morphine challenge to post-addict rats was followed by an EEG and behavioral arousal for as long as 180 minutes, the degree of which was less pronounced at the longer intervals following withdrawal. The EEG and behavioral arousal of the post-addict rat in response to morphine challenge is reminiscent of similar responses in human post-addicts already reported and may further emphasize the pharmacodynamic factors in morphine addiction.

KHAZAN, N. and COLASANTI, B. EEG correlates of morphine challenge in post-addict rats. Psychopharmacologia 22: 56 (1971)

Adult female Sprague-Dawley rats were prepared with chronically implanted cortical and temporal muscle electrodes and i.v. cannulae. Morphine injections of 10 mg/kg were given i.p. to naive rats and to post-addict rats at successive intervals following morphine withdrawal. These intervals extended in a few cases up to one year. In the naive rat, high voltage EEG slow bursts associated with stuporous behavior appeared almost immediately after injection and prevailed for 60-90 min. This phase was followed by continuous EEG and behavioral arousal for another period of 60-90 min. after which sleep appeared. In contrast, morphine challenge to post-addict rats was followed by an EEG and behavioral arousal for as long as 180 min, the degree of which was less pronounced at the longer intervals following withdrawal. The EEG and behavioral arousal of the post-addict rat in response to morphine challenge is reminiscent of similar responses in human post-addicts already reported and may further emphasize the pharmacodynamic factors in morphine addiction.

KHAZAN, N. and COLASANTI, B. Protracted rebound in rapid eye movement sleep time and electroencephalogram voltage output in morphine dependent rats upon withdrawal. The Journal of Pharmacology and Experimental Therapeutics 183(1): 23 (1972)

Rats prepared with chronic electrodes for recording the direct and voltage-integrated cortical electroencephalogram (EEG) as well as the integrated electromyogram were made dependent on morphine by its administration through chronic indwelling i. v. cannulas. Injections of morphine sulfate were given automatically at an initial dose of 1.25 mg/kg/hr for 24 hours. This dose was increased on successive days to 2.5, 5, 10 and 20 mg/kg/hr respectively. After maintenance of the rats on the highest dose for two days, the injections were discontinued. EEG and electromyogram recordings monitored continuously revealed a suppression of rapid eye movement (REM) sleep during morphine administration at the progressively increasing doses; on the second day of the 20 mg/kg/hr dose, however, the duration of REM sleep returned to the control base-line value. The mean EEG voltage output of REM sleep episodes within these two days showed a slight but significant reduction. Within the first four to six hours after the withdrawal of morphine, the duration of REM sleep was significantly enhanced. After this initial elevation, both the duration and the mean EEG voltage output of REM sleep episodes declined to minimal levels during the remainder of the first day of withdrawal and remained below the control base-line values up to the third day. A significant rebound then occurred in both pamareters, during which the REM EEG voltage output was significantly elevated until the sixth or ninth day after withdrawal, while the rebound in REM time remained evident up to the 12th day. The increases in REM sleep time during this period of morphine abstinence extended to twice the REM rebound normally expected to follow REM deprivation by other means.

KHAZAN, N. and ROEHRS, T. EEG responses to morphine test dose in morphine and methadone treated rats. The Pharmacologist 15: 168 (1973)

We have reported that EEG responses to a test dose of morphine are markedly different in rats previously exposed to morphine from those in naive rats. In the present study, methadone is evaluated in a similar manner. After implantation with chronic electrodes for recording of the EEG and EMG, two groups of five rats each were given an i.p. dose of either 10 mg/kg morphine or 2 mg/kg methadone, respectively. A second injection at the same dose level was administered one week later. A third group of five rats were simultaneously treated with isotonic saline. Ten days after the last injection, all rats were given an i.p. test dose of 10 mg/kg morphine. In the saline-treated rats, this morphine injection induced high voltage EEG slow bursts in association with stuporous behavior appearing almost immediately and prevailing for 60 to 90 minutes Such administration to the rats having prior exposure to either morphine or methadone, however, resulted in a significant shortening of this period of EEG slow bursts and the stuporous phase by 50 to 75%. These EEG findings suggest comparable and long-lasting CNS effects produced by these narcotics.

KHAZAN, N. and ROEHRS, T. Methadone dependence and abstinence: EEG study in the rat. Drug Addiction: Neurobiology and Influences on Behavior, Vol III. Edited by J. H. Singh and h. Lal. New York: Stratton Intercontinental Medical Book Company, 1974.

The present EEG study was undertaken to compare states of dependence and abstinence in methadone and morphine treated rats and to assess the possible existence of a protracted REM sleep rebound in the methadone abstinent rat similar to that which has been reported tn the morphine withdrawn animal.

KIMIZUKA, H. and ABOOD, L.G. Interfacial adsorption of psychotomimetic drug using liquid scintillation. Journal of Pharmaceutical Sciences 62(5): 740-745 (May, 1973)

For abstract, see Section I. Methodology of Drug Research.

KIPLINGER, G.F. and MANNO, J.E. Dose-response relationships to cannabis in human subjects. Pharmacological Reviews 23(4): 339 (1971)

KLAUSNER, H.A., WILCOX, H.G. and DINGELL, J.V. Investigation of the plasma binding of tetrahydrocannabinol and other drugs by zonal ultracentrifugation. Presented at the Fifth International Congress on Pharmacology, San Francisco, California. 1972.

KNAPP, S. and MANDELL, A.J. Narcotic drugs: Effects on the serotonin biosynthetic systems of the brain. Science 177: 1209-1211 (1972)

The effects of short- and long-term administration of morphine on the activity of two measurable forms of rat brain tryptophan hydroxylase were studied. Morphine administration produced an immediate decrease and a long-term increase in the nerve ending (particulate) enzyme activity but did not change the cell body (soluble) enzyme activity. Cocaine administration demonstrated a short-term decrease in measurable nerve ending enzyme activity that was due to the inhibition of the high affinity uptake (the Michaelis constant, Km, is 10^{-5} molar) of trytophan, the serotonin precursor. Cocaine did not affect the low affinity uptake (K_m= 10^{-3} molar) of tryptophan. Both the uptake of the precursor and the enzyme activity appeared to be drug-sensitive regulatory processes in the biosynthesis of serotonin.

KNAPP, S., MANDELL, A.J. and GEYER, M.A. Effects of amphetamines on regional tryptophan hydroxylase activity and snaptosomal conversion of tryptophan to 5-hydroxytryptamine in rat brain. The Journal of Pharmacology and Experimental Therapeutics 189(3): 676-689 (1974)

For abstract, see Section II. Drug Chemistry and Metabolism,

KOPELL, B.S., TINKLENBERG, J.R. and HOLLISTER, L.E. Contingent negative variation amplitudes: Marihuana and alcohol. Archives of General Psychiatry 27: 809 (1972)

In a double-blind study, the amplitude of the contingent negative variation (CNV) was assessed in 12 normal men given placebo and quantified "social" doses of 1-delta-9-transtetrahydrocannabinol (THC) and alcohol (ethyl alcohol). Using subjects as their own controls, it was found that THC selectively enhanced the amplitude as compared to placebo while alcohol depressed it.

KOPELL, B.S. and WITTNER, W.K. The effects of chlorpromazine and methamphetamine on visual signal-from-noise detection. Journal of Nervous and Mental Disease 147(4): 418 (1968)

KOSERSKY, D.S., DEWEY, W.L. and HARRIS, L.S. Antipyretic, analgesic and anti-inflammatory effects of delta-9-tetrahydrocannabinol in the rat. European Journal of Pharmacology 24(1): 1 (1973)

The effects of body temperature produced by graded doses of delta-9-tetrahydrocannabinol (THC) and phenylbutazone (PB) were compared in both normal and pyretic rats. Dose related hypothermic responses were produced in normal animals given THC. THC reduced elevated temperatures in yeast-induced pyretic rats to near normal levels at doses which exhibited little hypothermic activity in normal rats. The oral antipyretic potency of THC was twice that of PB. The oral anti-inflammatory efficacy of THC was compared with PB and acetylsalicylic acid. THC was ineffective in inhibiting carrageenin-induced edema of the rat paw following acute or chronic administration.

KOSTERLITZ, H.W., LESLIE, FM. and WATERFIELD, A.A. Narcotic agonist and antagonist potencies of a homologous series of N-alkyl-norketobemidones measured by the guinea pig ileum and mouse vas deferens methods. Journal of Pharmacology 27: 73-78 (1975)

For abstract, see Section I. Methodology of Drug Research.

KOSTERLITZ, H.W. and WATERFIELD, A.A. An analysis of the phenomenon of acute tolerance to morphine in the guinea-pig ileum. British Journal of Pharmacology (in press)

KOSTERLITZ, H.W. and WATERFIELD, A.A. In vitro models in the study of structure activity relationships of narcotic analgesics. Annual Review of Pharmacology (in press)

KUBENA, R.K., PERHACH, J.L., JR., and HERBERT, B., III. Corticosterone elevation mediated centrally by delta-1-tetrahydrocannabinol in rats. European Journal of Pharmacology 14(1): 89-92 (1971)

For abstract, see Section II. Drug Chemistry and Metabolism.

KUPFER, D.J. and BOWERS, M.B., JR. REM sleep and central monoamine oxidase inhibition. Psychopharmacologia 27: 183 (1973)

Our preliminary observations on the relationship of sleep and lumbar CSF acid monoamine metabolite levels suggested a greater decrease in lumbar CSF HVA as compared to 5HIAA following clinical doses of phenelzine in the presence of virtually total REM suppression. This report on nine psychiatric patients confirms these findings in a larger sample and thus supports an inhibitory role for dopamine or other catecholamines in REM sleep mechanisms. The drug-withdrawal results indicate that the four patients with REM rebound showed increases in HVA levels compared to treatment levels, while the single patient with no REM rebound also had no increase in HVA levels.

LABRECQUE, G. and DOMINO, E.F. Tolerance to and physical dependence on morphine: Relation to neocortical acetylcholine release in the cat. The Journal of Pharmacology and Experimental Therapeutics 191: 189-200 (1974)

LAHIRI, P.K., LADDU, A.R. and HARDMAN, H.R. Effect of delta-9-THC on the heart rate of the dog. Federation Proceedings 31: 505 (1972)

The effect of THC, i.v., was studied in conscious (C) and in anesthetized (A) dogs. In C dogs graded doses of THC ranging from 0.012-2.0 mg/kg, produced a dose dependent bradycardia. A significant reduction in HR was observed with doses of 0.05-2.0 mg/kg. In both C and A groups THC (2 mg/kg) reduced HR equally. The effect of THC was reduced by pretreatment (PT) with propranolol (P) 2.0 mg/kg but more so after atropine methyl nitrate (AMN) 0.5 mg/kg. The effect was abolished after PT with a combination of AMN and P. Similar abolition of effect was observed after Cl transection of spinal cord. In the isolated supported heart preparation (ISHP) THC was ineffective.

LAL, H. and PURI, S.K. Morphine-withdrawal aggression: Role of dopaminergic stimulation. Drug Addiction: Experimental Pharmacology, Vol 1. Edited by J. M. Singh, L. H. Miller and H. Lal. Mount Kisco, New York: Futura Publishing Company, 1972.

It is a matter of common knowledge that, epidemiologically, heroin addiction is related to crimes of violence. However. neither is a cause-and-effect relationship established; nor is it known whether the violence is incidental to the methods of procuring heroin or is elicited by neuronal changes caused by heroin addiction. In order to obtain answers to these questions, we studied aggressive behaviors in animals made dependent on morphine. This paper will summarize the data from our laboratory which show that intense aggression can be obtained in animals during morphine-withdrawal and further suggest that aggression during morphine-withdrawal is due to the hyperactivity of central dopaminergic receptors. The role of dopaminergic stimulation in eliciting aggressive behaviors was suggested in a previous study with non-addicted mice.

LALLEY, P.M. and BAKER, W.W. Local analysis of endogenous cholinergic tremor mechanisms in the caudate nucleus. The Pharmacologist 9: 253 (1967)

Our group described the cholinergic mechanisms in tremor resulting from intracaudate injection of carbachol in chronic cats; this tremor was readily suppressed by locally administered catecholamines. To gain insight into the endogenous mechanisms, acetylcholine (ACh) activity was augmented by intracaudate injection of DFP or echotheopate (ECHO). Both anticholinesterase induced tremor of variable intensity and duration which was antagonized by local injections of epinephrine or dopamine. In contrast to carbachol, DFP (25-60 mu-g) and ECHO (15-30 mu-g) tremor activity was accompanied by local electrographic discharges which projected to functionally related areas. Tremor persisted for days to weeks after a single dose of DFP; tremorogenic susceptibility to small doses of ACh (10 mu-g) could be demonstrated even after overt motor activity had declined. Variations in the intensity and persistence of tremor appear related to fluctuating levels of intrinsic ACh. Additional factors capable of influencing local cholinergic activity will be considered. We conclude that critical imbalances in local metabolic processes regulating the dynamids of ACh, as well as catecholamines, both can result in tremor.

LANG, D.W., DARRAH, H.K., HEDLEY-WHYTE, J. and LAASBERG, L.H. Uptake into brain proteins of ^{35}S-methionine during morphine tolerance. The Journal of Pharmacology and Experimental Therapeutics (in press)

LEE, H.K. and WANG, S.C. Mechanism of morphine-induced miosis in the dog. The Journal of Pharmacology and Experimental Therapeutics (in press)

It was observed that dogs under 50% nitrous oxide and succinylcholine exhibited a moderately large pupil, maintained a good pupillary light reflex, and had a relatively high sensitivity to the miotic effects of morphine. A cumulative dose of 1 mg/kg i.v. of morphine caused marked and sustained miosis in these animals. Morphine 1 mg was found to have no pupillary effect by intra-ocular administration. Optic nerve section and cervical sympathectomy did not interfere with the miotic response in either acute or chronic preparations. Conversely, a cumulative i.v. dose of 30 mg/kg of morphine failed to cause pupillary constriction when oculomotor innervation had been interrupted. In addition, morphine, 0.2 to 0.6 mg/kg i.v., caused marked miosis in dogs whose occipital lobes or cerebral hemispheres had been removed. These findings suggest that morphine acts on a subcortical region causing constriction of the pupil. The possible location was ascertained by unit recording with micro-electrodes. It was observed that pupilloconstrictor neurons in the visceral nuclei of the oculomotor nuclear complex responded to morphine 0.2 mg/kg i.v., by increased frequency of discharge. Other neurons in the pupillary light reflex pathway showed depressed activity. Levallorphan, 0.05 mg/kg i.v., but not phenylephrine (locally applied to the conjunctival sac) antagonized all of the actions of morphine on the pupillo-constrictor neurons. The present findings demonstrate that the miosis induced by morphine is accomplished by an excitatory action of the narcotic on the visceral nuclei of the oculomotor nuclear complex.

LEVINE, R., ZAKS, A., FINK, M. and FREEDMAN, A.M. Levomethadyl acetate: Prolonged duration of opioid effects, including cross-tolerance to heroin in man. Journal of the American Medical Association 226(3): 316 (October, 1973)

One way to reduce diversion of methadone is to substitute a long-acting opioid such as levomethadyl acetate hydrochloride. In male volunteers, levomethadyl acetate was given three times weekly in increasing dosages, and blockade to 25 mg intravenously given heroin at 72 hours was determined. Levomethadyl acetate hydrochloride, 70 mg, was necessary to suppress subjective discomfort of withdrawal, and 80 mg or more to blockade pupillary effects. For clinical trials, levomethadyl acetate hydrochloride, 80 mg, three times a week is suggested as a substitute for methadone.

LEVY, J.A., MUNSON. A.E., HARRIS, L.S. and DEWEY, W.L. Effects of delta-8- and delta-9-tetrahydrocannabinol on the immune response in mice. The Pharmacologist (in press)

Skin graft survival (BDF skin on WYLAR mice) was determined following treatment with delta-9-tetrahydrocannabinol (THC) bound to bovine serum albumen (BSA). Delta-9-THC (25-200 mg/kg) was administered daily by gavage for 7 days prior to and until rejection of skin grafts. Graft survival for BSA-controls was 16.2 + 0.8 (SEM) days. Delta-9-THC increased graft survival time 21% to 42% over controls. In studies to determine the effect of delta-8- and delta-9-THC on IgM response to sheep erthrocytes (sRBC), drugs were administered orally with and for 7 days following i.p. injection of 0.1 ml of 20% suspension of sRBC. 200 mg/kg delta-9-THC reduced the hemagglutanin titer 72% as compared to controls. Similar results were obtained for delta-8-THC. Treatment of mice with delta-9-THC (25-200 mg/kg) daily for 7 days did not alter the functional activity of the reticuloendothelial system as measured by the vascular clearance of colloidal carbon. Phagocytic indices were .057 + .007 (SEM) for vehicle control and .049 + .005 for 200 mg/kg delta-9-THC.

LIN, C.H., BRAVERMAN, S., KEINATH, S., TRESK, R. and ADLER, M.W. Anticonvulsant action of acute morphine administration in rats. Federation Proceedings (in press)

LIN, S.C., SUTHERLAND, V. C. and WAY, E.L. Brain amino acids in morphine tolerant and non-tolerant rats. Proceedings of the Western Pharmacological Society 16: 8-13 (1973)

LINTS, C.E. and HARVEY, J.A. Altered sensitivity to foot shock and decreased brain content of serotonin following brain lesions in the rat. Journal of Comparative and Physiological Psychology 67: 23-31 (1969)

Rats with lesions in the ventrolateral tegmentum which ablated 50% of the medial lemniscus, the presumed primary projection system for pain, demonstrated a decreased sensitivity to electric shock as measured by an 84% elevation of the mean jump threshold. Lesions in the medial forebrain bundle, septal area, or dorsomedial tegmentum increased sensitivity to electric shock and decreased brain concentrations of serotonin. The septal area and dorsomedial tegmentum are strongly interconnected via the medial forebrain bundle by both ascending and descending fibers. It was concluded that lesions in this anatomical system increased sensitivity to electric shock by virtue of their effects on telencephalic serotonin and that serotonin normally functions to inhibit effects of a painful stimulus.

LINTS, C.E. and HARVEY, J.A. Drug-induced reversal of brain damage in the rat. Physiology and Behavior 4: 29-31 (1969)

Lesions in the medial forebrain bundle of the rat produced both an increased sensitivity to electric-foot shock and a decrease in the telencephalic content of scrotonin. Administration of DL-5-hydroxytryptophan reversed the effects of the lesion on shock sensitivity. Only L-5-hydroxytryptophan, the immediate precursor of scrotonin in brain, was effective. Equimolar dosages of either D-5-hydroxy-tryptophan or L-dihydroxyphenylalanine had no effect. It was suggested that sensitivity to a painful stimulus is in part determined by the telencephalic content of serotonin.

LIU, C-T. and ADLER, F.L. Immunological studies on drug addiction. I. Antibodies reactive with methadone and their use for detection of the drug. Journal of Immunology 111: 472 (1973)

LOMAX, P., GROSS, S.J. and CAMPBELL, C. Immunological blockade of the hypothermic effect of delta-9-tetrahydrocannabinol in the rat. Pharmacology and Thermoregulation. Edited by E. Schenbaum and P. Lan. White Plains, New York: Abert J. Phiebig, 1973. Pp. 488-490.

LOWNEY, L.I., SCHULZ, K.. LOWERY. P.J. and GOLDSTEIN, A. Extraction of a mouse brain proteolipid with opiate receptor properties. Committee on the Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council, 1974.

LOWNEY, L.I., SCHULZ, K., LOWERY. P.J. and GOLDSTEIN, A. Partial purification of an opiate receptor from mouse brain. Science 183: 749-753 (1974)

A proteolipid isolated from a lipid extract of mouse brain demonstrates stereospecific binding properties for levorphanol. It is present only in neuronal tissue and most abundant in the rhombencephalon. One component saturates at a concentration corresponding to ma ximum pharmacologic effect in vivo. The estimated mass is 60,000 daltons per bound opiate molecule.

LYON, M. Rostra1 forebrain lesions in relation to central stimulant and neuroleptic drug action. Journal de Pharmacologic 5 (Supplement II): 61 (1974)

The relevance of ventrobasal (s. rhinalis) cortex to preservative responding associated with frontal lesions in rats was assessed by: (1) neurological examination; (2) water-reinforced, two-lever alternation; (3) tilt-cage, shock-escape with extra responses punished. D-amphetamine (2.0 mg/kg) and dopamine (DA) receptor-blocker Spiramide (0,025-0.075 mg/kg) were used posoperatively with tilt animals to assess lesion effects upon DA -activated systems. Results indicated that, without drugs, ventrobasal and dorsolateral frontal lesions are not differentiated by neurological examination or tilt-cage testing, but they may differ on two-lever alternation. However, in the tilt-cage only the ventrobasal operates (1) under d-amphetamine gave signif. more punished (extra) responses than sham operates, (2) under d-amphetamine plus Spiramide (0.075 mg/kg) reduced responses and shock-free time signif. below control levels. Neural systems dependent upon DA transmission may be more closely related to ventrobasal than to dorsolateral frontal cortex.

McAULIFFE, W.E. and GORDON, R.A. A test of Lindesmith's theory of addiction: The frequency of euphoria among long-term addicts. American Journal of Sociology 79(4): 795-840 (January, 1974)

For abstract, see Section I. Methodology of Drug Research.

McCLUNG, R., DAFNY, N. and BURKS, T.F. Effects of morphine and naloxone on CNS field in unanesthetized rats. Federation Proceedings (in press)

For abstract, see Section I. Methodology of Drug Research.

McMAHON, E.M., ANDERSEN, D.K., FELDMAN, J.M. and SCHANBERG, S.M. Methamphetamine-induced insulin release. Science 174: 66-68 (1971)

Administration of methamphetamine or amphetamine to rats and mice produces a rapid increase in the level of immunoassayable plasma insulin not attributable to hyperglycemia. While in the mouse this release of insulin is followed consistently by a profound hypoglycemia, in the rat this response is variable. Studies in vitro demonstrate that insulin is released by a direct effect of methamphetamine on the pancreas.

McMAHON, T., FELDMAN, J. and SCHANBERG, S.M. Further studies of methamphetamine-induced insulin release. Toxicology and Applied Pharmacology (in press)

McMILLAN, D.E. and DEWEY, W.L. On the mechanism of tolerance to delta-9-THC. Current Research in Marihuana. Edited by M.F. Lewis. New York: Academic Press, 1972.

McMILLAN, D.E., DEWEY, W.L., TURK, R.F., HARRIS, L.S. and MCNEIL, J.H., JR. Blood levels of ^{3}H-delta-9-tetrahydrocannabinol and its metabolites in tolerant and nontolerant pigeons. Biochemical Pharmacology 22: 383-397 (1973)

For abstract, see Section II. Drug Chemistry and Metabolism.

McMILLAN, D.E., FORD, R.D., FRANKENHEIM, J.M., HARRIS, R.A. and HARRIS, L.S. Tolerance to active constituents of marihuana. Archives internationales de Pharmacodynamie et de Therapie 198: 132 (1972)

A marked pharmacological tolerance develops to the repeated administration of a number of behaviorally active cannabinoids. This tolerance is characterized by a rapid development and by the magnitude of the effect. Cannabinoid tolerance occurs in a number of species and cross tolerance among the cannabinoids appears to be widespread. Although the degree of tolerance development to the cannabinoids resembles that seen with morphine. we did not observe cross tolerance between morphine and delta-g-THC.

MAICKEL, R.P., BRAUNSTEIN, M.C., McGLYNN, M., SNODGRASS, W.R. and WEBB, R. W. Behavioral, biochemical, and pharmacological effects of chronic dosage of phenothiazine tranquilizers in rats. The Phenothiazines and Structurally Related Drugs. Edited by I.S. Forrest, C.J. Carr and E. Usdin. New York: Raven Press, 1974.

For abstract, see Section I. Methodology of Drug Research.

MAICKEL, R.P., LEVINE, R.M. and QUIRCE, C.M. Differential effects of d- and 1-amphetamine on spontaneous motor activity in mice. Research Communications in Chemical Pathology and Pharmacology 8(4): 711-714 (August, 1974)

For abstract, see Section I. Methodology of Drug Research.

MAICKEL, R.P. and MALONEY, G.J. Effects of barbital on deprivation-induced water consumption by rats. Physiology and Behavior 8: 1175-1178 (1972)

Treatment of water-deprived rats with barbital in doses of 20-160 mg/kg I.P., evoked an increase in water consumption. The pretreatment time, especially with the largest dose, was critical. Pretreatment of 15 minutes or less caused an increase in water consumption despite a decreased motor activity; a 45 min pretreatment time decreased water consumption. while increased drinking was observed with 8 or 20 hr pretreatments. The content of sodium in sodium barbital had a significant stimulatory effect on drinking at the 5 min pretreatment time.

MAICKEL. R.P., ROMPALO, A.M. and COX, R.H., JR. Differential effects of monoamine oxidase inhibitors. Research Communications in Chemical Pathology and Pharmacology 8(4): 727-730 (August. 1974)

For abstract. see Section I. Methodology of Drug Research.

MANDELL, A.J. Frontiers in the neurobiology of euphoria. American Handbook of Psychiatry, Vol. VI. Edited by S. Arieti, D.A. Hamburg and H.K. H. Brodie. New York: Basic Books, 1972.

For abstract, see Section I. Methodology of Drug Research.

MANDELL, A.J. Neurobiological barriers to euphoria. American Scientist 61(5): 565-573 (September-October, 1973)

The brain seems well equipped to counter chemical perturbation whether the agent is exogenous (a psychoactive drug) or endogenous (a natural amine gone awry).

MANDELL, A.J. Neurochemical aspects of narcotic addiction -- A conceptual review. Proceedings of the Fourth International Conference on Methadone. Edited by A. Goldstein. New York: NAPAN, 1972.

MANDELL, A.J., editor. New Concepts in Neurotransmitter Regulation. New York: Plenum Press, 1973.

For abstract, see Section II. Drug Chemistry and Metabolism.

MANDELL, A.J., KNAPP, S. and HSU, L.L. Minireview. Some factors in the regulation of central serotoenergic synapses. Life Sciences 14: 1-17 (1974)

For a number of years release, reuptake, vesicular storage, and degradation via monoamine oxidase were the exclusive foci in chemical studies of the regulation of central serotonergic synapses. This brief review describes some other factors, including the brain levels of tryptophan and uptake processes in the nerve ending relevant to the substrate, the activity and amount of tryptophan hydroxylase in cell bodies and nerve endings, and a potential regulatable parasynaptic inactivation process, N-methylation. In chronic and acute drug studies some of these factors appear to function to compensate for acute perturbations in central serotonergic synaptic processes.

MANDELL, A.J., SEGAL, D.S. and KUCZENSKI, R. Metabolic adaptation to antidepressant drugs -- A neurochemical paradox. Catecholamines and Behavior. Edited by A. Friedhoff. New York: Plenum Press, 1974.

MANDELL, A.J., SEGAL, D.S. and KUCZENSKI, R. Metabolic adaptation to antidepressant drugs - Implications for pathophysiology and treatment in psychiatry. Catecholamines and Behavior. Edited by A. J. Friedhoff. New York: Plenum Press, 1974.

MANDELL, A.J., SEGAL, D.S., KUCZENSKI, R.T. and KNAPP, S. Amphetamine-induced changes in the regulation of neurotransmitter biosynthetic and receptor functions in the brain. Pharmacology and the Future of Man, Vol. 1. San Francisco: Karger, Basel, 1973. Pp. 95-105.

MANNO, B.R. and MANNO, J.E. 11-hydroxy-delta-9-tetrahydrocannabinol induced changes in the perfused rat heart. Presented at the Meeting of the Society of Toxicology, Williamsburg, Virginia, Spring, 1975.

For abstract, see Section I. Methodology of Drug Research.

MANNO, B.R. and MANNO, J.E. The marihuana dilemma: Has it been resolved? Toxicology Annual. Edited by C. L. Winek. New York: Marcel Dekker. Inc. (in press)

MANNO, B.R. and MANNO, J.E. Some cardiovascular actions of delta-9-tetrahydrocannabinol in the rat. Toxicology and Applied Pharmacology 25: 451 (1973)

For abstract, see Section I. Methodology of Drug Research.

MANNO, J.E. and MANNO, B.R. Cardiovascular actions of 11-hydroxy-delta-9-tetrahydrocannabinol in the rat. Presented at the Meeting of the Society of Toxicology, Williamsburg, Virginia, Spring, 1975.

Eleven-hydroxy-delta-9-tetrahydrocannabinol (11-OH-THC), dissolved in a vehicle of 5% ethanol, 1.5% Tween-80 and water (Olsen, et al. (1973) J. Pharm. Pharmac, 25, 344.) was administered intravenously or subcutaneously to male, albino rats in doses of 0.025 mg/kg, 0.05 mg/kg and 0.15 mg/kg Direct arterial blood pressure and heart rate were continuously monitored via indwelling femoral arterial catheters from the unanesthetized, unrestrained animals for 90 minutes after drug administration. A similar series of experiments was conducted to investigate the effect of pretreatment with the metabolic inhibitor, SKF-525A (beta-diethylaminoethyl diphenylpropylacetate) administered 30 minutes before the 11-OH-THC.

The administration of 11-OH-THC by either the intravenous or subcutaneous route did not produce any significant alteration in cardiovascular response in animals not pretreated with SKF-525A. In animals that were pretreated with SKF-525A there was an immediate positive chronotropic effect up to +10% of control at the 0.05 mg/kg 11-OH-THC dose. There was a negative chronotropic action at the 0.15 mg/kg dose that returned back to control values after the intravenous dose. The positive and negative chronotorpic actions occurred when the drug was administered either intravenously or subcutaneously. The data indicate a biphasic action of 11-OH-THC on heart rate and support implication of the compound in the marihuana induced tachycardia observed in man.

MANNO, J.E. and MANNO, B.R. The interaction of delta-9-tetrahydrocannabinol (THC). pentobarbital and SKF-525A with the cardiovascular system of the rat. Federation Proceedings 32: 755 (1973)

For abstract, see Section I. Methodology of Drug Research.

MANNO, J.E., MANNO, B.R. and KIPLINGER, G.F. Motor and mental performance with marihuana: Relationship to administered dose of THC and its interaction with alcohol. Behavioral Actions of Marihuana. Edited by L.L. Miller New York: Academic Press (in press)

MARKS, M.J. and MEDZIHRADSKY, F. Characterization of the active transport of benzomorphans in leukocytes. Proceedings of the Fifth International-Congress on Pharmacology, San Francisco, July 23-28, 1972.

MARSHALL, I. and SMITH, C.B. The role of tyrosine hydroxylase in changes in brain catecholamine synthesis after acute and chronic administration of morphine to mice. Committee on the Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council, 1973. P. 351.

MARTIN, B.R., DEWEY, W.L. and HARRIS, L.S. Subcellular distribution of 3H-delta-9-tetrahydrocannabinol in brains of nontolerant and tolerant rats. Proceedings of the Sixth International Congress of Pharmacology, Helsinki, Finland, July 20-25 (in press)

For abstract, see Section II. Drug Chemistry and Metabolism.

MARTIN, B.R., DEWEY, W.L., HARRIS, L.S. and BECKNER, J. Marihuana-like activity of new synthetic tetrahydrocannabinols. Pharmacology Biochemistry and Behavior (in press)

For abstract, see Section II. Drug Chemistry and Metabolism.

MARTIN, B.R., HARRIS, L.S., DEWEY, W.L., MAY, E.L. and WILSON, R.S. Behavioral and pharmacological properties of 11-methyl- and 9-nor-delta-8-tetrahydrocannabinol. Federation Proceedings 33(3, Part I): 540 (March, 1974)

It has been demonstrated that delta-8-tetrahydrocannabinol (THC), is rapidly metabolized to 11-hydroxy-delta-8-THC in the body, and it has been postulated that this metabolite is responsible for the activity of delta-8-THC. The pharmacological properties of 2 analogs of delta-8-THC, 11-methyl- and 9-nor-delta-8-THC were investigated. The former is probably not converted to an 11-hydroxy metabolite, the latter cannot be. In the unanesthetized dog these analogs produce a cannabinoid like effect on overt behavior. They produce prance like placement of feet, static ataxia, hyperreflexia and a decrease in spontaneous activity. This profile of behavior is the same as that seen after delta-8- or delta-9-THC. In the anesthetized dog 9-nor-delta-8-THC is again as effective as delta-8-THC in producing bradycardia and hypotension; as before. 11-methyl-delta-8-THC is somewhat less effective. In mice delta-8-THC, 9-nor-delta-8-THC, and 11-methyl-delta-8-THC have no effect on hexobarbital induced sleeping time and exhibit no antinbciceptive activity as measured in the tail flick or hot plate test. Each compound has some activity in the phenylquinone writhing test, delta-8-THC being more active than either analog.

MASUR, J. and KHAZAN, N. Induction by cannabis sativa (marihuana) of rhythmic spike discharges overriding REM sleep electrocorticogram in the rat. Life Sciences 9: 1275-1280 (1970)

Cannabis sativa and delta-9-tetrahydrocannabinol (delta-9-THC) have been shown to disrupt complex memory patterns in rhesus monkeys and to interfere with visual discrimination in both monkeys and pigeons. These drugs alter maze learning, bar pressing, and climbing rope performances, and after chronic treatment in food-deprived rats, they induce aggressiveness. Administration to mice of delta-9-THC is followed by a slight increase in whole-brain concentration of 5-hydroxytryptamine. Cerebral norepinephrine concentration appears to decrease after low doses and to increase after high doses.

Changes in the electroencephalogram (EEG) and in the sleep-awake cycle have been reported to occur after administration of psychotropic drugs to experimental animals and to man. Studies on the acute effects of Cannabis indica resin on the EEG of the rabbit revealed initial stimulation and subsequent depression, followed by a recovery phase during which repeated high voltage sharp waves weremanifest. In humans deprived of REM sleep for two nights, REM time tended to be decreased by marihuana extract, THC or synhexyl (a synthetic analogue of THC), but the change was not significant. In normal subjects. THC had no consistent effect on REM sleep time.

The present study describes acute and chronic marihuana-induced changes in the electrocorticogram during longitudinal study of the sleep-awake cycle in the rat.

MECHOULAM, R. Cannabinoid chemistry. Marijuana. Chemistry, Metabolism, Pharmacology and Clinical Effects. Edited by R. Mechoulam. New York: Academic Press, 1973. Pp. 1-88.

MECHOULAM, R. Chemistry and cannabis activity. Ciencia e Cultura 25(8): 742 (1973)

MECHOULAM, A. Marihuana chemistry. Review. Science 168: 1159 (1970)

MECHOULAM, R., BEN-ZVI. Z., AGURELL, S., NILSSON, I.M., NILSSON, J.L.G., EDERY, H. and GRUNFELD, Y. Delta-6-tetrahydrocannabinol-7-oic acid, a urinary delta-6-THC metabolite: Isolation and synthesis. Experientia 29: 1193 (1973)

MECHOULAM, R., BEN-ZVI, Z. and GAONI, Y. Hashish XIII. On the nature of the Beam test. Tetrahedron Letters 24: 5615 (1968)

For abstract, see Section II. Drug Chemistry and Metabolism.

MECHOULAM, R., BEN-ZVI, Z., SHANI, A., ZEMLER, H., LEVY. S., EDERY, H. and GRUNEFELD, Y. Cannahinoids and cannabis activity. Cannabis and Its Derivatives. Pharmacology and Experimental Psychology. Edited by W.D.M. Paton and J. Crown. Fairlawn, New Jersey: Oxford University Press, 1972.

MECHOULAM. R., BEN-ZVI, Z., VARCONI, H. and SAMUELOV, Y. Cannabinoid rearrangements. Synthesis of delta-5-tetrahydrocannabinol. Tetrahedron Letters 29: 1615-1619 (1973)

For abstract, see Section II. Drug Chemistry and Metabolism.

MECHOULAM, R., BEN-ZVI, Z., YAGNITINSKY, B. and SHANI, A. A new tetrahydrocannabinolic acid. Tetrahedron Letters 28: 2339 (1969)

MECHOULAM, R., BRAUN, P. and GAONI, Y. Hashish XI. A stereospecific synthesis of (-)-delta-l- and (-)-delta-$1^{(6)}$-tetrahydrocahnabinol. Journal of the American Chemical Society 89: 4552 (1967)

MECHOULAM. R., BRAUN, P. and GAONI, Y. Synthesis of delta-l-tetrahydrocannabinol and related cannabinoids. Journal of the American Chemical Society 94: 6159 (1972)

For abstract, see Section II. Drug Chemistry and Metabolism.

MECHOULAM, R. and EDERY, H. Structure-activity relationships in cannabinoid series. Marijuana. Chemistry, Metabolism, Pharmacology and Clinical Effects. Edited by R. Mechoulam. New York: Academic Press, 1973. Pp. 101-133.

MECHOULAM, R. and GAONI, Y. Hashish X. The absolute configuration of delta-l-tetrahydrocannabinol, the major active constituent of hashish. Tetrahedron Letters 12: 1109-1111 (1967)

MECHOULAM. R. and GAONI, Y. Recent advances in the chemistry of hashish. Progress in the Chemistry of Organic Natural Products (Fortschritte der Chemie Organischer Naturstoffe). Edited by L. Zechmeister. New York: Springer-Verlach-Verlag, 1967.

MECHOULAM, R., SHANI, A., EDERY, H. and GRUNFELD, Y. Chemical basis of hashish activity. Science 169: 611-612 (1970)

A sample of hashish was extracted consecutively with petroleum ether, benzene, and methanol. When tested intravenously in monkeys only the petroleum-ether fraction was active. This material was further fractionated. The only active compound isolated was delta-l-tetrahydrocannabinol. Cannabinol, cannabidiol, cannabichromene, cannabigerol, and cannabicyclol when administered together with delta-1-tetrahydrocannabinol do not cause a change in the activity of the latter, under the experimental conditions used. These results provide evidence that, except for delta-1-tetrahydrocannabinol, no other major, psychotomimetically active compounds are present in hashish.

MECHOULAM, R., SHANI, A., YAGNITINSKY, B., BEN-ZVI, Z., BRAUN, P. and GAONI, Y. Some aspects of cannabinoid chemistry. Botany and Chemistry of Cannabis. Edited by C.R.B. Joyce and S.H. Curry. London: J. and A. Churchill, 1970. Pp. 93-117.

MECHOULAM, R., VARCONI, H., BEN-ZVI, Z., EDERY, H. and GRUNFELD, Y. Synthesis and biological activity of five tetrahydrocannabinol metabolites. Journal of the American Chemical Society 94: 7930 (1972)

MECHOULAM, R. and YAGEN, B. Stereoselective cyclizations of cannabinoid 1, 5 dienes. Tetrahedron Letters 60: 5349 (1969)

MECHOULAM, R., YAGNITINSKY, B. and GAONI, Y. Hashish XII. Stereoelectronic factor in the chloranil dehydrogenation of cannabinoids. Total synthesis of dl-cannabichromene. Journal of the American Chemical Society 90: 2418 (1968)

MEDZIHRADSKY, F., MARKS, M.J. and CARR, E.A., JR. Energy-dependent uptake of benzomorphans by leukocytes. Biochemical Pharmacology 21: 1625-1632 (1972)

For abstract, see Section Ii. Drug Chemistry and Metabolism.

MEDZIHRADSKY, F., MARKS, M.J. and METCALF, J.I. Cellular transport of CNS drugs in leukocytes. Narcotic Antagonists. Edited by M.C. Braude, L.S. Harris, E.L. May, J.P. Smith, and J.E. Villarreal. Advances in Bibchemical Psychopharmacology, Volume 8. New York: Raven Press, 1973. Pp. 537-548.

Using leukocytes as model mammalian cells, the cellular transport of various CNS drugs was studied. Morphologically intact and metabolically active rat. leukocytes rapidly accumulated pentazocine against a concentration gradient by a process which fulfills the criteria for an active transport. The energy for the transport is derived from anaerobic metabolism of glucose. The kinetics of the process are characterized by a rapid initial uptake: 5 sec after addition of the drug 60% of the final cellular drug concentration was reached; saturation was usually obtained between 2 and 3 min. When pentazocine was present in the medium at micromolar concentrations, the cellular accumulation of the drug was fivefold. The maximum velocity of the uptake was 0.12 mu-moles/g cells/5 sec and the concentration of drug necessary to achieve half-maximum velocity (K_m) was 40 mu-m. The temperature coefficient of the transport process was constant at four drug concentrations and three temperatures: a temperature change of 10° C affected the uptake by a factor of two. The transport of pentazocine was competitively inhibited by analogue bcnzomorphans and its cellular uptake was blocked by inhibitors of anaerobic glycolysis. The active transport of pentazocine was independent of the presence of sodium and not affected by ouabain. In addition to pentazocine, methadone and morphine were also accumulated at a rapid rate into leukocytes. The cells showed marked selectivity in their uptake of these compounds. The highest affinity for the cellular accumulation, characterized by a K_m of 10 mu-M, was observed with methadone, whereas morphine was actively transported inot leukocytes with a much lower affinity: its Km was 4 mM. Ouabain had no effect upon the uptake of morphine and methadone. The results suggest the existence in the plasma membrane of leukocytes of transport systems responsible for the cellular accumulation of various CNS drugs.

MEDZIHRADSKY, F. and NANDHASRI, P.S. Effects of some analgesics and antidepressants on the (Na^+ + K^+)-adenosine triphosphatase from cortices of brain and kidney. Biochemical Pharmacology 21: 2103-2109 (1972)

For abstract, see Section II. Drug Chemistry and Metabolism.

MESHEL, E. and DENBER, H.C. Double-blind study of tybamate in psychotic patients. Diseases of the Nervous System 28: 311-313 (1967)

MILLER, J.M. and COCHIN, J. Dose-related aspects of tolerance to the analgesic effect of chronically administered morphine sulfate (MS) in mice. The Pharmacologist 10: 189 (1968)

It is known that irregular and even infrequently repeated doses of narcotic analgesics result in analgesic activity lower than that elicited by an initial dose of the same size, and that the tolerance that develops is influenced by dose size and schedule. In order to quantitate some of these aspects of the altered response to chronic drug administration, 8 mg/kg and 6 mg/kg MS were administered SC to two groups of 12 male mice (ICR strain) 18 times over 26 days and again on day 63. Analgesia was measured on various days during the 26 day period and on day 63 by the hot plate method of Eddy and Leimbach (JPET 107: 385, 1953). Differences were seen in the rate of development, degree, character and persistence of tolerance. A mean analgesic effect significantly (P less than. 05) lower than the initial day's effect was seen in the 8 mg/kg group on the 5th day while it was not until day 25 that a comparable attenuation was seen in the 6 mg/kg group. The day 63 test showed that the effect of an 8 mg/kg dose was only 58% of the initial day's level, while the 6 mg/kg group no longer demonstrated significant tolerance. An interesting observation was that from day 5 to the conclusion of the test a greater analgesic effect was seen after 6 mg/kg MS than after 8 mg/kg.

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MISRA, A.L. and MULE, S.T. Persistence of methadone-^{3}H and metabolite in rat brain after a single injection and its implications on pharmacological tolerance. Nature 238: 155-156 (July 21, 1972)

MISRA, A.L, and MULE, S.J. Stereoselectivity and differential metabolism in vivo of dextro and laevo -methadone-1-^{3}H. Nature 241: 281-283 (January 26, 1973)

MISRA, A.L., MULE, S.J., BLOCH, R. and VADLAMANI, N.L. Physiological disposition and metabolism of Levo-methadone-1-^{3}H in nontolerant and tolerant rats. The Journal of Pharmacology and Experimental Therapeutics 185(2): 287-299 (1973)

For abstract, see Section II. Drug Chemistry and Metabolism.

MIZOCUCHI, K. and MITCHELL, C.L. An evaluation of the effects of morphine on electrocortical recruitment in the cat and dog. The Journal of Pharmacology and Experimental Therapeutics 166: 134-145 (1969)

The effects of morphine on recruiting responses in the cat and dog have been studied with several stimulating sites. These sites were the thalamic nuclei centrum medianum, medialis dorsalis, centralis medialis and ventralis anterior. The recording sites were on the anterior sigmoid, posterior sigmoid, anterior ectosylvian, posterior lateral and posterior suprasylvian gyri, as well as in the nucleus ventralis anterior. The morphine dosage was 1, 2 and 4 mg/kg. It was found that recruiting responses generally were depressed in the cat after morphine, although this was not statistically significant in all cases. In the dog recruiting responses were likewise generally depressed, although a tendency toward enhancement was sometimes seen. However, the most striking effect of morphine on recruiting responses in the dog was an alteration in the recruitment pattern (waxing and waning of the response). This was not observed in the cat. Presumptive evidence is presented on which are based working hypotheses concerning the effects of morphine on the diffuse thalamocortical projection system.

MOLANDER, L. and RANDRUP, A. Investigation of the mechanism by which L-DOPA induces gnawing in mice. Acta Pharmacologica et Toxicologica 34: 312-324 (1974)

Stereotyped behaviour including gnawing was elicited in mice by L-DOPA given after various doses of the decarboxylase inhibitor Ro 4-4602. The gnawing was estimated quantitatively. The effect of various drugs including reserpine, FLA-63. spiramide and alpha-methyltyrosine on the gnawing was studied and it is concluded that the gnawing is influenced by both dopamine and noradrenaline in the brain. The relation of noradrenergic brain mechanisms to gnawing seems to be complicated.

MORETON, J.E. and DAVIS, W.M. Effects of delta-9-tetrahydrocannabinol on locomotor activity and on phases of sleep. The Pharmacologist 12(2): 258 (1970)

Rats injected daily s. c. with 25 mg/kg of synthetic delta-g-tetrahydrocannabinol (THC) in olive oil and placed for 4 hrs in photocell actometers showed initially a biphasic response of stimulation during the 1st hour and depression during the 2nd. The excitant effect was no longer seen by the 4th day. With continued doses through 20 days, tolerance developed to the depressant effect by the 11th day, and lasted through at least the 9th day after withdrawal. Mice injected i.p. for 23-26 days with 50 mg/kg of THC in a 2% Tween-65, 2% Arlacel-20, 1% olive oil, and saline suspension showed a twofold reduction in locomotor inhibitory response to THC. Rats chronically implanted with electrodes over the frontal cortex, and in the dorsal hippocampus and neck muscles were given one 10 mg/kg dose of THC i.p. following control recordings. THC caused a pronounced reduction in the level of paradoxical sleep (PS) which required two days for complete recovery. In rats selectively deprived of PS for 72 hrs, 10 mg/kg of THC caused a blockade of PS rebound.

MORETON, J.E. and DAVIS, W.M. Electroencephalographic study of effects of delta-g- and delta-8-tetrahydrocannabinol and cannabis estract on sleep in the rat. The Pharmacologist 13(2): 246 (1971)

The criteria for paradoxical sleep (PS) included activated ECoG. hippocampal (HIP) theta rhythm, rapid eye movement (EM) and low EMG. Daily 3h recordings were made from 3 days before to 6 days after the drugs. in non-deprived (ND) rats and for 6 days afterwards in rats PS deprived (PSD) for 72 h. Five and 10 mg/kg of synthetic delta-9 and delta-8-tetrahydrocannabinol (delta-9-THC and delta-8-THC) and 10 mg/kg of cannabis extract i.p. ↓ PS, ↓ slow sleep (SS) and ↑ wakefulness in ND rats. PS rebound was blocked in PSD rats. Ten mg/kg delta-9-THC in studies utilizing recordings 24 h/d on the daily schedule as above suppressed PS for 12 h in 2/3 ND rats. A non-significant rise in PS occurred in the next 12h. In PSD rats 10 mg/kg suppressed PS for 6-9 h and ↑ SS. Rebound did not occur in the next 12 h or subsequent 5 days. Ten mg/kg delta-9-THC, daily for 20 days to rats permitted PS only during daily 15h EEG sessions, reduced PS for 3 days after which tolerance developed. No PS rebound occurred in the 10 day post-drug period. Ten mg/kg on the 13th withdrawal day tended to reduce PS. After THC, sleep characterized by HIP theta rhythm, cortical spindles, low EM and or absent EM occurred. If such is considered PS, then THC reduces PS in ND and has little effect in PSD rats.

MORETON, J.E. and DAVIS, W.M. Electroencephalographic study of the effects of tetrahydrocannabinols on sleep in the rat. Neuropharmacology 12: 897-907 (1973)

This study examined the effects of tetrahydrocannabinols on sleep-wake states, and especially on paradoxical sleep (PS), in rats bearing chronically implanted EEG and EMG electrodes. Greatest attention was given to delta-g-tetrahydrocannabinol (delta-9-THC) but delta-8-tetrahydrocannabinol and marihuana extract distillate were also studied. These agents in i.p. doses of 5 and 10 mg/kg reduced PS in rats non-deprived (ND) of PS, caused an apparent dissociation of phasic and tonic events of PS in PS-deprived (PSD) rats, and tended to decrease slow wave sleep and increase wakefulness. No PS rebound was detected during 5 post-drug days in ND rats. In PSD rats the normal PS rebound was replaced by a form of "incomplete PS" characterized by tonic hippocampal theta thythm, absence of muscle activity and continuous cortical spindling in the absence of normal phasic activity. The effect of 10 mg/kg of delta-9-THC administered daily for 20 days was initially to suppress PS; this was followed by rapid development of tolerance to effects on both sleep and behavior. Partial tolerance remained upon retesting at the 13th withdrawal day. When delta-9-THC was withdrawn no PS rebound occurred in rats. In preliminary experiments in cats, single doses of delta-9-THC (10 mg/kg i.p.) caused a clear-cut inhibition of PS in both ND and PSD cats which was followed by a significant PS rebound on the first post-drug day.

MORETON, J.E., ROEHRS, T. and KHAZAN, N. Sleep-awake activity and self-injection pattern of rats dependent on morphine, methadone, or L-alpha-acetyl-methadol (LAAM). Federation Proceedings 33: 516 (1974)

We have reported on the EEG, EMG and sleep-awake activity of dependent rats maintained by voluntary i.v. self-injections of morphine on a fixed-ratio schedule of reinforcement (Khazan, Weeks, and Schroeder, JPET, 155, 521, 1967). The usual inter-injection interval was 2-3 hours. Sleep and REM sleep predominated before an injection, and wakefulness with EEG slow bursts followed the injection. In our present studies, when methadone (2 mg/kg/injection) or LAAM (1 mg/kg/injection) was substituted for morphine (10 mg/kg/injection), rats titrated the daily drug intake and maintained the dependence state. A significant shift from inter-injection intervals of 2.5 ± 0.1 hours for morphine to shorter intervals of 1.4 ± 0.1 hours was noted for methadone and to much longer intervals for LAAM (8.8 ± 0.8 hours). While the drug-induced pattern of distribution of sleep, REM sleep, and awake during these inter-injection intervals was analogous, LAAM exhibited a relatively delayed onset of this effect. However. EEG slow bursts that may represent a significant agonistic property emerged with little delay following LAAM injections.

MUDGILL, L., FRIEDHOFF, A.J. and TOBEY, J. Effect of intraventricular administrations of epinephrine. norepinephrine, dopamine, acetycholine, and physostigmine on morphine analgesia in mice. Archives internationales de Pharmacodynamie et de Therapie 210: 85 (1974)

Intraventricular epinephrine or norepinephrine antagonized the analgesic effect of morphine on the rat tail flick response while dopamine in equivalent doses had no effect. The effects of acetylcholine or physostigmine were not definitive.

MULE, S.J. and CLOUET, D.H. Pharmacological and biochemical aspects of opiate dependence. Psychopharmacologia 26: 116 (1972)

For abstract, see Section II. Drug Chemistry and Metabolism.

MUNKVAD, I. The mechanism of action of psychopharmacological agtens on behaviour. Acta Pharmacologica et Toxicologica 35 (Supplement I): 11 (1974)

The problem of aggressiveness and abnormal social behaviour can be elucidated from an anatomical, a behavioural, and a biochemical point of view.

1) Anatomy: regions in the brain related to rage, aggressiveness, fear and escape have been investigated for many years. Rage is produced by lesions or electro-stimulation in many parts of the brain, but a system in the central gray matter of the mid-brain and hypothalamus seems to be of special importance. These are areas in which a high concentration of noradrenaline is found.

Some experiments, however, indicate that forms of aggressive features depend on dopamine in the basal ganglia. In this relation it should be mentioned that direct bilateral intrastriathl injections of L-Dopa after MAO-inhibition in rats are able to produce aggressive behaviour.

The behavioural effects of treatment with L-Dopa in man underline this statement, as agitation, restlessness, and aggressiveness in one form or another is not a quite uncommon side-effect in Parkinsonian patients treated with this drug.

Munkvad, I. continued

2) Behaviour: while lower doses of amphetamine (5 mg/kg) in mice produce stereotypies, higher doses of this drug (15 mg/kg) add aggressive activities during certain experimental circumstances and these activities are counteracted by neuroleptics, especially the more specific ones with high antidopaminergic action.

In rats aggressive behaviour can be produced by apomorphine, but also by amphetamine combined with inhibitors of noradrenaline synthesis, indicating a role of dopamine in relation to aggressiveness.

In monkeys the social behaviour is altered with small doses of amphetamine and especially neuroleptics with strong anti-dopaminergic action are able to normalize the animals to some degree. Here also dopamine seems to play a role.

In man amphetamines can produce aggressive behaviour, and neuroleptics, which all have antidopaminergic properties in various degree, can normalize the abnormal behaviour including the stereotypies.

3) Biochemistry: in rats and other animals it is difficult to distinguish behaviourally between different types of aggression and it is possible that different biochemical mechanisms in various brain areas give rise to nearly identical aggressive behaviour and attempt to "normalize" these different forms of aggressiveness with neuroleptics depends on a very subtle alteration of a balance between transmitters as noradrenaline, dopamine, serotonin and acetylcholine, perhaps with "moderators" as e.g. gamma-aminobutyric acid.

Neuroleptics in animals and also in man are able to modify abnormal social behaviour (including aggressiveness), interfering with the balance between the different transmitters in various parts of the brain, including the dopaminergic system in corpus striatum.

MUNKVAD, I., PAKKENBERG, H. and RANDRUP, A. Aminergic systems in basal ganglia associated with stereotyped hyperactive behavior and catalepsy. Brain, Behavior and Evolution 1: 89-100 (1968)

The physiological action of the basal ganglia is still far from being understood. The evidence indicates, however, a motor regulatory role as well as a role in the integration of "higher" behavior.

Experiments from recent years have provided new knowledge about the occurrence and distribution of biogenic amines in the basal ganglia.

These aminergic systems seem to be associated with stereotyped hyperactive behavior and catalepsy produced by amphetamine and neuroleptic drugs.

It is suggested as a working hypothesis that the aminergic systems in basal ganglia may play an important role in the adtipsychotic effect of neuroleptic drugs and perhaps in the pathogenesis of schizophrenia.

MUSHLIN, B. and COCHIN, J. Effects of irradiation on the development of tolerance to morphine in the rat. Federation Proceedings 33:502 (1974)

A number of studies have been carried out in our laboratory characterizing the effects of cycloheximide, Freund's adjuvant and dose interval on the development of tolerance. In order to investigate the phenomenon of tolerance further, we conducted a series of experiments in which we irradiated groups of rats with gamma irradiation (1250 R), either before or during a regimen of morphine sulfate (MS) injections (15 mg/kg subcutaneously). Non-irradiated control groups were tested concomitantly. The difference in the degree of tolerance development between irradiated and control groups was compared by measuring morphine effect using the hot-plate assay. Rats irradiated and then given daily MS injections starting 24 hours after irradiation were not different from controls with respect to tolerance development after 4 injections. Thus irradiation seemingly has no effect on the development of tolerance under these conditions. However, when rats were irradiated, given bone marrow transplants, and then weekly injections of MS starting 6 days after irradiation, there was a significant delay in the development of tolerance as compared with control animals. In another experiment, irradiation of animals that had previously received 4 weekly injections of MS failed to affect subsequent development of tolerance induced by additional weekly injections of MS.

MUSHLIN, B., GRELL, R. and COCHIN, J. Blockade of the development of tolerance to morphine by concurrent naloxone administration. The Pharmacologist 16: 193 (1974)

The effects of concurrent morphine (MS) and naloxone (NAX) administration on the development of tolerance to MS in Wistar-Lewis rats were examined., MS dosage was 15 and NAX 6 mg/kg s.c. Rats were assigned to 3 groups: MS only, receiving MS daily for 9 days; NAX only, NAX for 8 days and MS on the ninth day; and MS-NAX, both NAX and MS for 8 days and MS only on the ninth day. NAX was given 10 min before, and 50 and 110 min after MS; rats not receiving MS were given saline. Animals were tested on the hot plate on days 1 and 4, following the usual dose of MS or saline. On day 9, all rats were injected with just MS and tested for analgesic response. In a second experiment, NAX injections were given 30 and 10 min before, and 50 and 110 min after MS or saline. All injections were given weekly rather than daily. Rats received 2 injections of MS or NAX or MS-NAX and all received only MS on their last injection. Animals were tested on the hot plate after each MS or saline injection. In neither experiment did NAX or MS-NAX treatment induce any tolerance to MS, nor were there any differences between the analgesic response of NAX or MS-NAX groups. Concurrent administration of NAX and MS appeared to block both MS analgesia and tolerance development.

NAKAMURA, J., HENDERSON, G.L. and WINTERS, W.D. The behavioral and EEG effects of 1-alpha-acetylmethadol (LAAM) in the rat. Proceedings of the Western Pharmacological Society 17: 155-158 (1974)

L-alpha-acetylmethadol (LAAM), a long-acting synthetic congener of methadone, has recently undergone preliminary trials in the treatment of heroin addicts. The 72-96 hour duration of action of LAAM allows the patient to receive maintenance doses of the drug every third day instead of daily as with methadone.

The purpose of this study is to determine the gross behavioral and EEG activity in rats after the administration of LAAM.

NAKAMURA, J. and MITCHELL, C.L. A comparison of the effects of morphine and pentobarbital on conditioned and non-conditioned bioelectrical potentials evoked within the pyriform lobe. Archives internationales de Pharmacodynamie et de Therapie 206: 31-40 (1973)

The effects of morphine sulfate and pentobarbital sodium were studied in cats on bioelectrical potentials evoked by stimulation of the pyriform cortex and recorded in the entorhinal cortex. The effects of a 1000 msec conditioning stimulus applied to radial nerve at 5 and 40 v, to tooth pulp at 5 and 100 v, to the reticular formation at subthreshold, threshold and suprathreshold voltage intensities for cortical activation and to radical nerve at threshold levels, were examined. The conditioning with greatest effect in, raising blood pressure and activating the cortex produced the greatest inhibition of the entorhinal response. Pentobarbital caused a general depression of both conditioned and non-conditioned responses. In contrast, morphine had no effect on the integrity of the non-conditioned response, However, it did antagonize the inhibitory effect of the more noxious levels of the conditioning stimuli. It was suggested that the removal by morphine of the specific inhibition of the entorhinal response after noxious conditioning stimuli may be related at least in part to the mechanism of morphine analgesia.

NAKAMURA, J. and MITCHELL, C.L. The effects of morphine, pentobarbital and chlorpromazine on bioelectric potentials evoked in the brain stem of the cat by electrical stimulation of the gingiva and tooth pulp. The Journal of Pharmacology and Experimental Therapeutics 178: 232 (1971)

The effects of morphine sulfate (1, 2 and 4 mg/kg), pentobarbital sodium (2.5, 5 and 10 mg/kg), chlorpromazine hydrochloride (1, 2 and 4 mg/kg) and saline (0.1, 0.2 and 0.4 ml/kg) on the responses evoked from the central tegmental fasciculus, the dorsal tegmentum of the mesencephalon and the spinal trigeminal tract by gingival and tooth pulp stimulation were studied. In the central tegmental fasiculus, morphine had no significant effect on responses evoked by either type of stimulus. Pentobarbital and chlorpromazine significantly depressed both responses. In the dorsal tegmentum. both responses were significantly depresse'd by morphine, but this effect was not dose related. Pentobarbital significantly depressed both responses in a dose-related manner. Chlorpromazine had no effect on the response elicited by gingival stimulation but depressed that produced by tooth pulp stimulation. In the spinal trigeminal tract, morphine had no effect on the responses evoked by either mode of stimulation. Pentobarbital and chlorpromazine slightly depressed the responses. The responses in the spinal trigeminal tract increased with time in the absence of drug. Had saline not been used to monitor the stability of the preparation an incorrect interpretation would have been placed on the results obtained with the recordings from the spinal trigeminal tract. The proper assessment of drug effects on bioelectrical responses is impossible without this control.

NAKAMURA, J. and MITCHELL, C.L. The effects of morphine, pentobarbital and saline on bioelectrical potentials recorded in limbic structures of the cat evoked by radial nerve and direct brain stimulation. Archives internationales de Pharmacodynamie et de Therapie 200: 70-87 (1972)

The effects of morphine, pentobarbital and saline were studied in cats on limbic and midbrain potentials recorded in 1) entorhinal cortex and mesencephalic reticular formation evoked by radial nerve stimulation and in 2) septum, hippocampus and entorhinal cortex after pathways were established from mesencephalic reticular formation to entorhinal, septum to hippocampus. hippocampus to septum and entorhinal, entorhinal to hippocampus and piriform cortex to entorhinal. Morphine had no effect on hippocampal or entorhinal excitability. However, morphine reduced

Nakamura, J. and Mitchell, C.L. The effects . . . on bioelectrical potentials recorded in limbic structures . . . continued

sensory input into these areas since entorhinal responses evoked by radial nerve or reticular stimulation were depressed but responses recorded from pathways within the limbic areas were not. Pentobarbital, in contrast, depressed the general level of excitability of both hippocampus and entorhinai cortex as well as the entorhinal response evoked by radial nerve and reticular stimulation. It. was concluded that morphine exhibits more specificity in its effect on limbic structures than that shown by pentobarbital.

NASH, P., COLASANTI, B. and KHAZAN, N. Long-term effects of morphine on the electroencephalogram and behavior of the rat. Psychopharmacologia 29: 271-276 (1973)

Adult female Sprague-Dawley rats were given 10 mg/kg i.p. injections of morphine sulfate twice weekly, at 84-h intervals, over a period of three weeks. A control group of rats was simultaneously treated with equivalent volumes of isotonic saline. The animals were then prepared with cortical and temporalis muscle electrodes. Ten days after the last injection of morphine or of saline, they were placed in individual cages for recording of the EEG and the EMG and both groups were given i.p. a 10 mg/kg test dose of morphine. In the saline-treated rats, high voltage EEG slow bursts in association with stuporous behavior appeared almost immediately after injection and prevailed for 60-90 min. This phase was followed by continuous EEG and behavioral arousal for another period of 60-90 min, after which sleep appeared. Administration of the 10 mg/kg test dose of morphine to the rats having prior morphine exposure resulted in a much shorter initial period of EEG and behavioral stupor and a longer secondary phase of EEG and behavioral arousal. The duration of the entire morphine effect as determined by the latency to sleep onset, however, was the same in the saline-treated and morphine-treated groups of rats. These results support the assumption that, long-term alterations in the function of the CNS occur not only after morphine addiction, but also after only exposure to morphine.

NEWMAN, L.M., LUTZ, M.P., GOULD, M.H. and DOMINO, E.F. Delta-9-THC and ethyl alcohol: Evidence for cross-tolerance in the rat. Science 175:1022-1023 (1972)

Rats trained in a one-way avoidance situation were made tolerant to the depressant effects of delta-9-tetrahydrocannabinol. Ethy1 alcohol (3. 2 grams per kilogram, infraperitoneally) did not greatly affect rats that were tolerant to delta-9-tetrahydrocannabinol but depressed the behavior of nontolerant rats. Rats made tolerant to ethyl alcohol were less affected by delta-9-tetrahydrocannabinol.

NICHOLSON, M.T., PACE, H.B. and DAVIS, W.M. Effects of marijuana and lysergic acid diethylamide on leukocyte chromosomes of the golden hamster. Research Communications in Chemical Pathology and Pharmacology 6(2):427 (September, 1973)

Female Syrian golden hamsters were given daily subcutaneous injections of marihuana extract distillate (MED), containing 17.1% delta-9-tetrahydrocannabinol (delta-9-THC), or dl-lysergic acid diethylamide (LSD) for 10 consecutive days. Daily dosages of MED, in terms of delta-9-THC content, were 1.0, 10, and 100 mg/kg. LSD dosages were 0.1, 10, 100. and 1000 mu-g/kg. A ninth drug treatment was the combination of MED at 100 mg/kg of delta-9-THC and 1000 mu-g/kg of LSD. None of these treatments caused significant elevation of leukocyte chromosome breaks above control levels.

NIELSEN, M. The effects of amitriptyline, desipramine, imipramine and protriptyline on the in vivo brain synthesis of ^{3}H-noradrenaline from ^{3}H-1-dopa in the rat. Acta Pharmacologica et Toxicologica 35(Supplement I): 43 (1974)

For abstract, see Section II. Drug Chemistry and Metabolism.

NIELSEN, M., EFLOV, L. and SCHEEL-KRUGER, J. The effect of amitriptyline, desipramine and imipramine on the in vivo brain synthesis of ^{3}H-L-dopa in the rat. Psychopharmacologia (in press)

NIELSEN, M., EPLOV, L. and SCHEEL-KRÜGER, J. Protriptyline induced inhibition of the in vivo ^{3}H-noradrenaline synthesis from ^{3}H-L-DOPA in the rat brain. Nanunyn-Schmiedebergs Archives of Pharmacology 285: 15-28 (1974)

NIELSEN, E.B. and LYON, M. Some possible mechanisms involved in amphetamine or apomorphine induced hypodipsia. Journal de Pharmacologic 5(Supplement II): 72 (1974)

Hypodipsia produced by d-amphetamine or apomorphine must be related in some, as yet unknown, way to deficits in cholinergic initiation of drinking. Both dopamine (DA) and norepinephrine may be implicated. Hypodipsia yielded by d-amphetamine (2.0 mg/kg) or by apomorphine (0.8 mg/kg) was partially antagonized by specific DA receptor-blockers (Pimozide and Spiramide) in doses which alone produced no drinking loss. Injections of adrenergic blockers aceperone (1.0 mg/kg) or phenoxybenzamine (10.0 mg/kgl, in rats pretreated with d-amphetamine (2.0 mg/kg) restored drinking to ca. 75% of NaCl control levels, while without d-amphetamine these doses had no effect. Like doses had no effect on hypodipsia following apomorphine (0.4 mg/kg). The results suggest that d-amphetamine and apomorphine affect drinking by different modes with apomorphine deficits being more specifically DA-related, since adrenergic blocking did not antagonize this type of hypodipsia.

NILAKANTAN, B. and RANDRUP, A. Phylogenetic approach to the study of brain mechanisms involved in the action of amphetamine and other drugs. Present Status of Psychotropic Drugs. Edited by A. Cerletti and F. Bove, Amsterdam, the Netherlands: Excerpta Medica Foundation, 1969.

NILSSON, I.M., AGURELL, S., NILSSON, J.L.C., OHLSSON, A., LINDGREN, J.E. and MECHOULAM, R. Metabolism of 7-hydroxy-delta 1(6)-tetrahydrocannaninol in the rabbit. Acta Pharmaceutics Suecica 10:97 (1973)

For abstract, see Section II. Drug Chemistry and Metbolism.

NILSSON, J.L.G., NILSSON, I.M., AGURELL, S., BEN-ZVI, Z. and MECHOULAM, R. Synthesi a potential urinary THC metabolite. Acta Pharmaceutics Suecica 9:215 (1972)

For abstract, see Section II. Drug Chemistry and Metabolism.

NYBACK, H., SCHUBERT, J. and SEDVALL, G. Effect of apomorphine and pimozide on synthesis and turnover of labelled catecholamines in mouse brain. Journal of Pharmacy and Pharmacology 22: 622-624 (1970)

OGLESBY, M.W., ROSENBERG, J. and WINTER, J.C. Behavioral and biochemical effects of chronic administration of bromide in the rat. Psychopharmacologia 32: 85-92 (1973)

Bromide, a sedative in low doses and a psychotogen in high doses and a psychotogen in high doses in man, was tested for behavioral and biochemical effects in the rat. The kinetics of bromide excretion following chronic administration were studied in the rat to determine drug regimens necessary to achieve stable, non-lethal levels of blood bromide. When administered daily to animals performing on a variable-interval schedule of positive reinforcement, a low dose of bromide increased rates of responding while a high dose depressed response rates. Following withdrawal of the drug after six weeks of administration, response rates returned to previously determined control levels. Chlorpromazine failed to antagonize bromide-induced rate depression. No change in the concentration of norepinephrine or 5-hydroxytryptamine was seen with any dose of bromide studied.

OVERTON, D.A. and WINTER. J.C. Discriminable properties of drugs and state dependent learning. Federation-Proceedings 33(7): 178-5-1786 (1974)

PACE, H.B., DAVIS, W.M. and BORGEN, L.A. Teratogenesis and marijuana. Annals of the New York Academy of Sciences 191: 123-131 (December, 1971)

PACE, H.B., HOLBROOK, J.M., TOMPOROWSKI, R.A. and DAVIS, W. M. Oral methadone treatment of pregnant female rats: Effects on neonatal viability and postnatal development. The Pharmacologist 16(2): 649 (1974)

Methadone hydrochloride in distilled water was administered p.o. to pregnant female rats (Wistar-derived) during discrete periods of gestation, and postpartum, to determine its effects on offspring viability and growth. Dosing schedules used were: 15 mg/kg on days 8-14(I), days 15-20(II) or day 15 to weaning (III). and 30 mg/kg on days 8-14(IV). Control females received, 1 ml/kg of vehicle. Offspring were weighed individually within 4 h after birth and daily until weaning. There were no differences among groups in the ave. wt. of pups at birth or the number of pups dead at birth. Group IV pups showed significantly lower values for ave. wt./pup and ave. litter size at weaning than controls. Only 29% of live-born group IV pups survived past 48 h compared to 80% of controls. Most of these neonatal deaths occurred within 24 h. Groups II and III also differed from control. having less pups alive at 48 h and at weaning. Group I showed no significant deviations from control values. Reflex ontogeny of methadone pups was somewhat delayed compared to controls.

PAKKENBERG, H., FOG, R. and NILAKANTAN, B. The long-term effects of perphenazine enanthate on the rat brain. Some metabolic and anatomical observations. Psychopharmacologia 29: 329-336 (19'73)

Perphenazine enanthate 3.4 mg/kg per injection, was administered subcutaneously to rats every second week over a period of a year, a total of 31 mg per animal being given. The animals were observed weekly and only a few became cataleptic during brief periods. After treatment for one year, ^{3}H-uridine and ^{3}H-lysine were administered intravenously and the labelling was studied by microautoradiography. Labelling of the cortical cells in the treated animals was found to be slightly greater than in the control animals. The converse was found in the basal ganglia in the case of uridine. None of these differences were significant.

In counting nerve cells in the cortex and in the basal ganglia, a significantly lower number of nerve cells was found in the basal ganglia in the treated group.

Histological investigation of lungs, liver, spleen and kidneys showed only insignificant changes in the tissues.

All the investigations mentioned were performed blind.

PAL, B.K., LOWNEY, L.I. and GOLDSTEIN, A. Further studies on the stereospecific binding of levorphanol by a membrane fraction from mouse brain. Agonist and Antagonist Actions of Narcotic Analgesic Drugs. Edited by H. W. Kosterlitz, H.O.J. Collier and J.E. Villarreal. Baltimore, Maryland: Baltimore University Park Press, 1973. Pp. 62-69

1. The stereospecific binding of the opiate levorphanol by mouse brain tissue in vitro is concentration dependent; about 3 x 10^{16} molecules per brain were bound at the highest concentration studied.

2. The binding capacity is not extractable by Triton X-100 or sodium lauryl sulphate. It is enhanced by EDTA and nearly abolished by calcium or magnesium ions. It is unaffected by p-chloromercuribenzoate, beta-mercaptoethanol, or iodoacetic acid. Trypsin treatment increases it.

3. The material responsible for the stereospecific binding is completely extactable into chloroform-methanol, and is recovered again in an 'aqueous residue' obtained by water extraction of the organic phase. The material has the general properties of a proteolipid.

PALMER, G.C., SULSER, F. and ROBISON, G.A. The effect of neurohumoral and adrenergic agents on cyclic AMP levels in various areas of the rat brain in vitro. Neuropharmacology (in press)

PANG, C.N., ZIMMERMANN, E. and SAWYER, C.H. Effects of morphine on the proestrous surge of luteinizing hormone in the rat. Proceedings of the 87th Annual Meeting of the American Association of Anatomists. Cleveland, Ohio, April, 1974.

Barraclough and Sawyer (Endocrinology 57: 329, 1955) reported inhibition of ovulation in the rat by administering morphine sulfate (MS) at the outset of the critical period on the afternoon of proestrus. To further study this inhibition, the influence of MS on the ovulatory surge of circulating luteinizing hormone (LH) was investigated. Normally cycling Sprague-Dawley adult rats were given various doses of MS intraperitoneally at 1400 on proestrus. Four hours later, jugular venous blood was collected under rapid ether anesthesia and used for radioimmunoassay determination of plasma levels of LH. To verify ovulation, the uterine tubes were examined the following day for the presence or absence of ova. Compared with low levels of LH observed at 1400 in 8 untreated proestrous rats,

Pang, C. N., Zimmermann, E. and Sawyer, C. H. continued
saline (S)-injected controls showed highly elevated (p less than 0.01) values of LH at 1800 that evening and all animals ovulated. Compared with S-treated animals, those receiving 10 mg/kg MS showed apparently enhanced (p less than 0.05) levels of LH and all rats in this group ovulated. In contrast, rats given 60 mg/kg MS showed complete suppression (p less than 0.01) of LH discharge and failed to ovulate. Rats given either 20 or 40 mg/kg MS showed intermediate levels of LH which did not differ from that of S-treated controls but were less than that of rats given 10 mg/kg (p less than 0. 05) and greater than that of rats given 60 mg/kg (p less than 0.05). Inspection of the data from individual animals revealed that 3 of 6 rats receiving 20 mg/kg and 5 of 13 receiving 40 mg/kg MS showed marked suppression of LH levels (159±54 ng/ml) and no tubal ova, whereas the remainder of animals in these groups had high levels of LH (1523±167 ng/ml) and 7 or more tubal ova. These findings suggest that MS exerts dose-dependent effects on secretion of LH with stimulation at low doses and inhibition at higher doses. In addition. the data suggest that MS may block, in an all-or-none fashion, brain mechanisms responsible for triggering the progestrous surge of MS in the rat. Studies are underway to explore further these neuroendocrine effects of MS.

PAPESCHI, R. The effect of ECT on dopamine-dependent behaviour and DA turnover. Psychopharmacologia 26: 45 (1972)

ECT given for seven days prior to the administration of reserpine, or alpha-methyl-p-tyrosine accelerated the onset of catalepsy. The catalepsy induced by reserpine or alpha-methyl-p-tyrosine is at least in part due to the depletion of dopamine. There was a correlation between the scores on catalepsy and the increase of HVA following reserpine. The onset of amphetamine-induced stereotyped behaviour was also accelerated by preliminary application of ECT. The effect of ECT on dopamine turnover was studied by means of synthesis inhibitors.

PAPESCHI, R. An investigation on the behavioral and hypothermic effects of yohimbine: Interaction with drugs affecting central and peripheral 'monoamines. Archives internationales de Pharmacodynamie et de Therapie 208: 61-80 (1974)

The hypothermia and the behavioral changes induced by yohimbine in the rat were investigated by studying the interaction of this alkaloid with various drugs which affect central and peripheral monoamines. The results indicated that hypothermia mainly stems from a peripheral blocking action of yohimbine on alpha adrenergic receptors, but a central component, through stimulation of serotonin receptors, may also exist. Although yohimbine seems to block noradrenaline functions also centrally, it is unlikely that this mechanism contributes to the hypothermia. The changes in body temperature induced by yohimbine and by the interacting drugs were not always correlated with those of motor activity. The implications of the present findings for the thermoregulatory function of central and peripheral monoaminergic neurons are discussed,

Yohimbine antagonized the aggressiveness and the increased locomotion induced by various drug treatments, such as pargyline Ro4-4602 + L-DOPA, thus suggesting that this alkaloid blocks central noradrenaline mechanisms too; on the other hand, only the stereotyped activity induced. by (+)-amphetamine was reduced by yohimbine, whereas that following apomorphine or Ro-4602 + L-DOPA was unaffected. This observation suggests that yohimbine may also disturb the intraneuronal metabolism of brain dopamine, though being inactive on dopamine receptors.

PAPESCHI, R. Relations of effects of neuroleptics in animals to pharmacological parkinsonism in man. Psychopharmacologia 26(Supplement): 21 (1972)

Parkinsonian syndrome is characterized by akinesia, rigidity and tremor and the same symptoms can be induced by neuroleptics in man. Neuroleptics can also induce a neurodysleptic syndrome and akathisia. Parkinson's disease in man is believed to be due to a lesion of the nigro-striatal pathway with low dopamine and HVA in striatum and CSF. The symptom which better correlates with a decrease of HVA in CSF is akinesia. There is evidence that also pharmacological syndromes induced by phenothiazines and butyrophenones in experimental animals are due to the blockade of dopamine receptors. Again in these syndromes the most striking feature is the reduced motor activity, which can arrive to catalepsy. Catalepsy can also be induced by other means interfering with the nigro-straital pathway such as lesions or block of synthesis of dopamine by alpha-methyl-p-tyrosine. However, in the latter case the toxicity of the drug itself is also in part responsible for the syndrome. Bulbocapnine and reserpine provide other examples of catalepsy related 'to interference with dopaminergic mechanisms. However, cholinergic stimulation can also provoke catalepsy. It is concluded that the main symptom induced by neuroleptics in animals and in man which correlates with the dysfunction of the dopaminergic nigro-straital pathway is the reduction of motor activity.

PAPESCHI, R., RANDRUP, A. and LAL, S. Effect of ECT on dopaminergic and noradrenergic mechanisms. I. Effect on the behavioural changes induced by reserpine, alpha-methyl-p-tyrosine or amphetamine. Psychopharmacologia 35: 149-158 (1974)

The preliminary application of one or 5-8 electroconvulsive shocks (ECT) significantly increased the severity of the seadation and catalepsy induced by reserpine or alpha-methyl-p-tyrosine (AMT). ECT X 7, prior to various doses of d-amphetamine, significantly depressed the locomotor stimulation and the rearing, and slightly antagonized the decrease of social interactions induced by this drug. No consistent effect was found on amphetamine-induced stereotyped activity. Locomotor activity was already depressed in the ECT group before amphetamine.

The results suggest that ECT cannot affect such spontaneous and drug-induced behaviour through an increased functional catecholamine turnover, but rather through a decreased flow of nerve impulses in catecholaminergic neuronal systems and/or through increased non-functional catecholamine turnover or other non-specific neurological changes.

PATRICK, G.A., DEWEY, W.L. and HARRIS, L.S. Relationship of brain morphine concentration to tail-flick activity in pellet-implanted and acutely treated mice and rats. Federation Proceedings 33(3): 474 (1974)

Brain morphine (M) levels were measured according to a modification of the fluorometric method of Kupferberg et al. (JPET 145: 247, 1964) in animals in which the tail-flick test was performed. In mice implanted subcutaneously with M pellets (75 mg), significant analgesia was observed 20 min. after implantation though brain M was not measurable. Increased analgesia paralleled increased brain M at 1 and 4 hours after implantation. By 24 hrs. analgesia had begun to decline and was entirely absent at 72 hrs., though brain M levels remained elevated through 78 hrs. When the M pellets were removed at 72 hrs., brain M declined steadily, returning to zero 6 hrs. later. These data suggest that the encapsulation observed around the pellet does not greatly interfere with the absorption of M. Brain M levels were found to correlate with s. c.

Patrick, G.A., Dewey, W.L. and Harris, L.S. continued
doses of morphine sulfate (MS) and tail-flick activity in mice and rats. In mice the brain M level at the ED-50 in the tail-flick test was approximately 100 ng/g tissue, while in rats the brain M level at the ED-50 was found to be 140 ng/g tissue. Following a single S. C. injection of 8 mg/kg of MS, mouse brain M levels peaked at 30 mm. after injection, corresponding to peak analgesic effect. In rats, an injection of 16 mg/kg S.C. produced peak brain M levels and peak analgesia at 45 to 60 min. after administration.

PATRICK, G.A., DEWEY, W.L. and HARRIS, L.S. Studies on morphine tolerance and dependence in mice and rats. Virginia Journal of Science 125: 102 (1974)

Chronic administration of morphine (M) to rodents leads to development of the phenomena of tolerance and dependence. Tolerance is characterized by decreased analgesic activity of M and dependence is characterized by a number of signs upon withdrawl of M, among which loss of body weight is most reliable. Mice were treated chronically by the implantation of a pellet containing M base, while rats were treated by continuous infusion of morphine sulfate. The analgesic effect of M was measured by means of the tail-flick test, and the concentration of M was measured by a standard fluorometric technique. Brain M levels corresponded quantitatively to analgesic effect on acute M administration in regard both to magnitude and to time course of effect. Tolerance development was observed after 24 hours of chronic treatment, and pronounced tolerance and dependence were apparent at 72 hours. Upon cessation of treatment in mice, brain M levels returned to baseline within 6 hours while significant tolerance persisted for at least 24 hours. Following M withdrawal in rats, a 20 to 25% loss in body weight was observed after 24 hours, however, this sign of dependence was implanted at the beginning of the infusion regimen. This latter finding is of theoretical and practical importance in the search for a better treatment of narcotic addiction.

PATRICK, G.A., DEWEY, W.L., HARRIS, L.S., DAVES, E.D. and NEUMANN, J.H. Relationship of brain morphine concentration to tail-flick activity and tolerance and dependence development in chronically infused rats. The Pharmacologist 16(2): 71 (1974)

For abstract, see Section II. Drug Metabolism and Chemistry.

PATRICK, G.A., DEWEY, W.L., SPAULDING, T.C. and HARRIS, L.S. Relationship of brain morphine levels to analgesic activity in acutely treated mice and rats and in pellet-implanted mice. The Journal of Pharmacology and Experimental Therapeutics (in press)

The relationship of brain morphine concentration, determined fluorometrically, to tail-flick activity was investigated following acute and chronic morphine treatment of mice and acute treatment of rats. Brain morphine levels were quantitatively related to analgesic effect on acute administration, with levels of 100 and 140 ng/g tissue corresponding to the ED-50 in mice and rats, respectively. Over a 90-minute time course following acute s.c. injection, the analgesic effect of morphine in the tail-flick test lagged slightly behind morphine brain level in both species. In mice implanted s.c. with. morphine pellets, significant analgesia and appreciable morphine brain levels appeared as early as 20 to 30 min. after implantation. Increased brain morphine corresponded to increased analgesia at 1 and 4 hr. after implantation. Tolerance was evident by 24 hr. after implantation and was maximal at 72 hr. Brain morphine remained elevated up to 144 hr.

Patrick, G.A., Dewey, W.L., Spaulding, T.C. and Harris, L.S. continued. after implantation even though substantial encapsulation of the pellet occured within 72 hr. If pellets were removed at 72 hr., brain morphine declined to control levels within 6 hr., but significant tolerance persisted for at least 24 hr. after pellet removal. These results demonstrate that morphine is being absorbed from the pellet up to 6 days after implantation and that the decreased analgesic activity observed in the latter times is due to tolerance to the narcotic and not to a decrease in absorption from the pellet.

PEARSON, J., RICHTER, R.W., BADEN, M.M., SIMON, E., HILLER, J. and GROVER-JOHNSON, N. Studies on sites of binding and effects of narcotics in the human brain. Proceedings of the VII International Congress of Neuropathology (in press)

PEDIGO, N.W., DEWEY, W.L. and HARRIS, L.S. Determination and characterization of the antinociceptive activity of intraventricularly administered acetylcholine in mice. The Journal of Pharmacology and Experimental Therapeutics (in press)

Antinociceptive activity of intraventricularly administered acetylcholine was quantitated in mice by the tail-flick and phenylquinone tests. Acetylcholine was administered intraventricularly under light ether anesthesia in a 5 ul volume of sterile saline and mice were retested ten minutes later. A dose-response curve was established for acetylcholine (LD50 7.3 ug) which was potentiated significantly by intraventricular neostigmine and blocked by intraperitoneal atropine but not by atropine methyl nitrate or mecamylamine. The antinociceptive effect of morphine was potentiated by intraventricularly administered acetylcholine. The acetylcholine-induced antinociception was blocked by five narcotic antagonists in the same rank order of potency in which they antagonized the effects of morphine. However, the sterospecificity of two narcotic antagonists, pentazocine and cyclazocine, was reversed in blocking acetylcholine and morphine induced antinociception. Tolerance was demonstrated with chronic intraventricular administrations of acetylcholine and cross tolerance in morphine-pretreated mice was observed. Animals tolerant to acetylcholine were not tolerant to the antinociceptive effects of morphine.

The results of this study have established the phonomenon of acetylcholine-induced antinociception and demonstrated similarities between this phenomenon and morphine-induced antinociception. These data implicate the possible involvement of central cholinergic mechanisms in the antinociceptive action of morphine.

PEDIGO, N.W., DEWEY, W.L., HARRIS, L.S. and ACETO, M.D. Antinociceptive activity of intraventricularly administered acetylcholine in mice. Federation Proceedings (in press)

Antinociceptive activity of intraventricularly (ivt.) administered acetylcholine (ACh) was quantitated in mice by the tail-flick (T.F.) and phenylquinone (P.P.Q.) tests. ACh was administered iv-t. under anesthesia in a 5 ul volume of sterile saline. Peak antinociceptive activity was observed at 10 mm. and only slight activity existed at 20 min. Ivt. injections of procaine and pentobarbital were inactive, while ivt. choline was only weakly active. Dose-response curves were established for ACh (ED50 7.3 ug in T.F. and 5.1 ug in P.P.Q.). ACh was potentiated significantly by ivt. neostigmine and blocked by i.p. atropine but not atropine methyl nitrate or mecamylamine. The antinociceptive effect of morphine (M) was potentiated by iv-t. ACh. The ACh effect was blocked by 5 narcotic antagonists in the same rank order of potency in which they antagonized the effects of M. However, the steriospecificity of 2 narcotic antagonists, pentazocine and cyclazocine, was reversed in blocking ACh and M induced antinociception. Tolerance was demonstrated with chronic ivt. administrations of ACh and cross tolerance was observed in M-tolerant mice. Animals tolerant to ACh were not tolerant to the effects of M. The results of this study have established the phenomenon of ACh induced antinociception and demonstrated both similarities and differences between this phenomenon and M-induced antinociception.

PETERSON, D.W. and SPARBER, S.B. Increased fixed-ratio performance and differential d- and l-amphetamine action following norepinephrine depletion by intraventricular 6-hydroxydopamine. The Journal of Pharmacology and Expkrimental Therapeutics 191(3): 349-357 (1974)

The intraventricular injection of 200 mu-g of 6-hydroxydopamine (6-OHDA) into rats trained to respond on a fixed-ratio 30 (FR 30) schedule of food reinforcement resulted in decreased response rates which returned to predrug rates after 8 days. The response rates then gradually increased and remained significantly greater for up to 156 days after the 6-OHDA treatment. Vehicle-injected control animals did not change their rates over this same period of time. While the 6-OHDA treatment did increase reinforced responding, it did not increase the number of unreinforced (extinction) responses or exploratory activity. The dose of 6-OHDA used depleted hypothalamic and midbrain-striatal norepinephrine (NE) measured 1 week later, but midbrain-striatal dopamine was unchanged, At the end of the behavioral study, $5\frac{1}{2}$ months later, NE levels had partially recovered and the extent of this recovery was positively correlated with the increased response rates. The suppression of the FR responding by d-amphetamine was not altered by the 6-OHDA treatment. When l-amphetamine was given to the same rats, the behavioral suppression was significantly attenuated in the group that had received 6-OHDA. These results suggest a relatively greater importance of NE in some of the operant behavioral actions of l-amphetamine than of d-amphetamine.

PETERSON, G.R. and SHUSTER, L. Effects of morphine on choline acetyltransferase and acetylcholinesterase in cultured mouse neuroblastoma. Proceedings of the Western Pharmacological Society 16: 129-133 (1973)

The neuroblastoma system affords an opportunity to investigate neuronal functions in vitro. Cultured neuroblastoma cells possess choline acetyltransferase (ChAc) and acetylcholinesterase (AChE) activities, both of which are thought to be regulatory enzymes in this system. In addition, there is evidence for the hypothesis that cholinergic mechanisms are involved in. the actions of narcotic drugs on neurons.

PETERSON, G.R., WEBSTER, G.W. and SHUSTER, L. Effect of narcotics on enzymes of acetylcholine metabolism in cultured cells from embryonic chick brains. Neuropharmacology 13: 365-376 (1974)

The addition of $2 \cdot 5 \times 10^{-4}$ M morphine sulphate to cultures of cells dissociated from the brains of chick embryos brought about 25-50% increases in the activities of neuronal choline acetyltransferase (ChA) and acetylcholinesterase (AChE). Narcotic drugs also increased the activities of these two enzymes in the brains of developing chicks in vivo.

The effects of morphine on the cultures were antagonized by naloxone but not by propranolol. Both L(+)-dextrorphan and D(-)-levorphanol produced similar increments in the enzyme activities of cultured cells.

The activities of ChA and AChE in cultured cells from embryos that had been previously exposed to narcotics were unaffected, by the addition of morphine to the cultures. Dissociated brain cells from treated embryos also exhibited tolerance to the inhibition of leucine incorporation by high concentrations of morphine.

PILLARD, R.C. Medical progress. Marihuana. New England Journal of Medicine 283: 294-303 (August, 1970)

PIRCH, J.H. and OSTERHOLM, K.C. Influence of alpha-methyltyrosine on enhancement of shuttle-box avoidance by marijuana and pentobarbital. Research Communications in Chemical Pathology and Pharmacology 8(2): 203 (June, 1974)

Marijuana extract administered orally at doses of 20 or 40 mg/kg of delta-9-THC enhanced shuttle-box performance of poorly performing rats. A similar effect was produced by 5 or 10 mg/kg of pentobarbital. given intraperitoneally. Pretreatment with alpha-methyltyrosine, 50 mg/kg, antagonized the facilitative effect of marijuana but not that of pentobarbital. The results indicate that the facilitative effect of marijuana on shuttle-box performance involves catecholamines and that the actions of marijuana and pentobarbital to enhance shuttle-box avoidance are exerted through different mechanisms.

PRUITT, D.B., GRUBB, M.N., JAQUETTE, D.L. and BURKS, T.F. Intestinal effects of 5-hydroxytryptamine and morphine in guinea pigs, dogs, cats and monkeys. European Journal of Pharmacology 26(2): 298-305 (May, 1974)

Intestinal introluminal pressure was measured in vivo in anesthetized guinea pigs, dogs, cats and monkeys. In guinea pigs; but not in the other species, the intestinal stimulatory effect of 5-hydroxytryptamine was antagonized by morphine. The 5-HT-blocking action of morphine in intestine seems to be unique to the guinea pig.

PURI, S.K., COCHIN, J. and VOLICER, L. Effect of morphine sulfate on adenylate cyclase and phosphodiesterase activities in rat corpus striatum. Life Sciences (in press)

The effect of morphine sulfate (MS) on adenylate cyclase (AC) and phosphodiesterase (PDE) activities in the rat striatum was investigated. MS produced a dose-dependent increase in basal AC activity and did not alter sodium fluoride-induced stimulation both in vivo (7.5-30 mg/kg, 1 hr pretreatment, i.p.) and in vitro (1-100mu-M). In vitro, when submaximal effective concentrations of dopamine and MS were combined, there was an additive effect. However, administration of MS in vivo did not alter dopamine-induced stimulation of AC activity. MS, in vitro and in vivo inhibited PDE activity in a dose-dependent manner only with the high substrate concentration (3.3×10^{-3} M cyclic AMP). Preliminary results from this study indicate that morphine affects the cyclic AMP system.

PURI, S.K., VOLICER, L. and COCHIN, J. Changes in the striatal adenylate cyclase (AC) activity after acute and chronic morphine sulfate (MS) administration. The Pharmacologist 16(2): 269 (1974)

MS affects the striatal dopaminergic system in rat brain. Since dopamine (DA)-sensitive AC has been found in the striatum, we investigated the effect of acute and chronic administration of MS on AC activity. AC activity was measured by the method of Krishna et al. (J. Phar. Exp. Therap. 163, 379, 1968) using ^{14}C-ATP as a substrate. Acute MS administration (7.5-30mg/kg, i.p., 1 hr pretreatment) produced a dose-dependent increase in AC activity. In vitro addition of MS (0.1-100 mu-M) also stimulated AC in a dose-dependent manner. MS, both in vivo and in vitro, did not alter NaF-induced stimulation of AC activity and did not block DA-induced stimulation. Naloxone, an MS antagonist, increased AC activity and failed to antagonize MS-induced stimulation. The rats made dependent on MS (maximum dose, 100 mg/kg, 3 times a day) showed an increase in

Puri, S.K., Volicer, L. and Cochin, J. continued
the basal AC activity. This activity remained elevated for 72 hrs and returned to control 96 hrs after the last MS injection. Addition of DA in vitro, which stimulated AC activity in non-dependent rats, did not stimulate AC activity during withdrawal. These results suggest that both acute and chronic MS administration affect the AC system.

QUOCK, R.M. and HORITA, A. Apomorphine: Modification of its hyperthermic effect in rabbits by p-chlorophenylalanine. Science 183: 539 (1974)

The hyperthermic response of rabbits to apomorphine. a dopaminergic agonist, is abolished by prior treatment with p-chlorophenylalanine. If such 5-hydroxytryptamine (5-HT)-depleted animals are administered a peripherally acting decarboxylase inhibitor plus 5-hydroxytryptophan, central stores of 5-HT are regenerated and the hyperthermic response to apomorphine is restored in part. The effects of apomorphine in rabbits with elevated concentrations of 5-HT are not different from those in control animals. The behaviorai effects of apomorphine appear to be constant in all groups of animals tested. It is suggested that the hyperthermic effects of apomorphine in rabbits require the presence of 5-HT.

QUOCK, R.M. and HORITA, A. The interaction of naloxone with apomorphine induced hyperthermia in rabbits. Proceedings of the Western Pharmacological Society 16: 68 (1973)

Apomorphine, a central dopaminergic agonist, has been demonstrated in our laboratory to cause a dose dependent hyperthermic response in rabbits. The fact that apomorphine, a non-analgesic derivative of morphine, also causes some narcotic analgesic like responses led us to investigate whether the hyperthermia induced by apomorphine was a purely dopaminergic response or also involved stimulation of some unidentified receptor sites acted upon by morphine.

The present report describes the interaction between the narcotic antagonist naloxone and apomorphine and of attempts to uncover the underlying mechanism of interaction.

RANDRUP. A. The neuroleptics. Pharmacology of Neuroleptive Drugs, Vol. 5. Edited by J. Bobon and P. Janssen. New York: Karger, 1970. Pp. 23-33.

RANDRUP. A. and JONAS, W. Brain dopamine and the amphetamine-reserpine interaction. Journal of Pharmacy and Pharmacology 19: 483-484 (July, 1967)

RANDRUP, A. and MUNKVAD, I. Biochemical, anatomical and psychological investigations of stereotyped behavior induced by amphetamines. Amphetamines and Related Compounds: Proceedings of the Mario Negri Institute for Pharmacological Research, Milan, Italy. Edited by E. Costa and S. Garattini. New York: Raven Press, 1970. Pp. 695-713.

Amphetamine elicits a highly stereotyped form of hyperactive behavior when given to mammalian and avian species in doses of 1 to 20 mg/kg. Experiments with rats have indicated that the stereotyped activity is produced by an effect of amphetamine upon dopamine in cropus striatum. New evidence, which supports this interpretation, is presented. This evidence includes biochemical analysis of the interaction of reserpine with various amphetamines, micro-injections of dopamine and p-hydroxyamphetamine into corpus striatum, etc.

The stereotyped behavior of rats has been subjected to more detailed psychological analysis and this has shown that amphetamine even in low doses produces a selective stimulation: some activities (e.g., locomotion, rearing, sniffing) are increased while others (e.g., grooming) are concurrently decreased. With higher doses the activation becomes gradually more selective; at 10 mg/kg the behavior consists only of continuous sniffing, licking or biting of a small area and thus has a highly stereotyped character. Learned behavior (lever-pressing for shock avoidance) may be blended into the stereotypy. Selective stimulation leading to extreme stereotypy was also observed in primate monkeys given amphetamine.

Amphetamines in larger doses in humans have produced psychoses with schizophreniform symptoms including stereotypy. It is, therefore, thought that study of abnormal behavior produced by amphetamine may be of interest for psychosis research. It is also hoped that these studies may contribute to the understanding of amphetamine addiction and of certain features of normal behavior (e.g., regulation of behavioral variability and excitation level).

RANDRUP, A. and MUNKVAD, I. Brain dopamine and amphetamine induced stereotyped behaviour. Acta Pharmacolosia et Toxicologia 25 (4): 62 (1967)

RANDRUP, A. and MUNKVAD, I. Correlation between specific effects of amphetamines on the brain and on behavior. Current Concepts on Amphetamine Abuse. Edited by E.H. Ellinwood Jr. and S. Cohen. Washington, D.C.: U.S. Government Printing Office, 1972.

Animal experiments on the pharmacological effects of amphetamines have been performed in our laboratory for several years, This research was originally inspired by the clinical reports about an “amphetamine psychosis,” and it was hoped that our investigation would yield new information about the brain mechanisms underlying such psychoses. From the outset we were interested in possible correlations between the effects of amphetamines on the central nervous system and their specific behavioral effects, particularly the elicitation of abnormal behavior. The purpose of this presentation is to review the correlations which have been uncovered thus far. Our own data on brain effects are mostly biochemical, although some data on anatomic localization are included.

RANDRUP, A. and MUNKVAD, I. Evidence indicating an association between schizophrenia and dopaminergic hyperactivity in the brain. Orthomolecular Psychiatry 1: 2-7 (1972)

The evidence indicating an association between schizophrenia and brain dopamine is of pharmacological nature. It emerges from studies of two classes of drugs: amphetamines which can produce a schizophrenic-form psychosis and neuroleptics which can antagonize psychotic symptoms in schizophrenic patients.

RANDRUP, A. and MUNKVAD, I. Mechanisms by which amphetamines produce stereotypy, aggression and other behavioural effects. VIII Congress Collegium International Neuro-Psychopharmacologicum, Copenhagen. Praha: Avicenum Press, 1972.

The dopaminergic systems in the forebrain(nucleus caudatus, putamen and some adjacent areas) appear to have effects, in mammals, on'many perhaps all types of behaviour, and these effects tend in the extreme to change the whole pattern of behaviour into a stereotyped, apparently aimless one. At the same time each type of behaviour e.g. locomotion, aggressive and other social activities, drinking, etc. appear to be influenced also by other brain systems. The behavioural effects of a drug, which like amphetamines acts on several brain systems (dopaminergic, noradrenergic, serotonergic and possibly others) are therefore bound to be complicated. For example: smaller doses of d-amphetamine cause increase in locomotion of rats while larger doses cause inhibition. The increased locomotion can be stereotyped, consisting in repetition of a fixed route in a restricted part of the cage. Brain dopamine plays a role in these locomotor effects, but locomotion is also influenced by brain noradrenaline. Recent findings about the mechanisms by which amphetamines produce their behavioural effects will be reviewed. Real and apparent contradictidns in the most recent publications about experiments with brain lesions will be discussed; the ektent of lesions in the striatum and the slow recovery of behaviour after such lesions seem to be important items in this context.

RANDRUP, A. and MUNKVAD, I. Mechanisms by which amphetamines produce stereotypy, agression /sic/ and other behavioural effects. Psychopharmacologia 26(Supplement): 37 (1972)

For abstract, see Section II. Drug Chemistry and Metabolism.

RANDRUP, A. and MUNKVAD, I. Pharmacological studies on the brain mechanisms underlying two forms of behavioural excitations: Stereotyped hyperactivity and "rage." Annals of the New York Academy of Sciences 159: 928-938 (1969)

The effects of excitant or stimulant drugs are often measured by apparatus recording "general activity" such as jitter cages, treadmills, or cages traversed by light beams. By these methods, quantitative data are obtained and the effects of various drugs and various doses can be compared. Stimulant drugs may, however, also differ qualitatively, with respect to the forms of behavior. Everett and Wiegand (1962) stress the importance of these qualitative differences, giving a drastic example of two drugs (5-hydroxytryptophane and 3,4-dihydroxyphenylalanine, DOPA), both of which were reported to produce "excitement" or "central excitation" when given after a monoamine oxidase inhibitor. The former of these drugs was, however, found to produce jerks, abduction of the limbs, tremor, and convulsions, while the latter produced increasing degrees of organized motor activity, increased irritability, and aggressiveness. Another example is found in a detailed study of some amphetamine derivatives performed with cats by Muller-Calgan & Hotovy (1961). In the doses used, amphetamine and a norcamphane derivative (H610) both produced increased running, but while H610 also enhanced hopping, climbing. and mewing, these activities were depressed by amphetamine.

Randrup, A. and Munkvad, I. Pharmacological studies on the brain. . . continued

In the present paper we shall describe two forms of strong drug-induced excitation: stereotyped hyperactivity and "rage." Evidence concerning the neural mechanisms underlying these forms of hyperactivity will also be presented and discussed.

RANDRUP, A. and MUNKVAD. I. Relation of brain catecholamines to aggressiveness and other forms of behavioural excitation. Aggressive Behaviour. Edited by S. Garattini and E.G. Sigg. Amsterdam, the Netherlands:. Excerpta: Medica Foundation, 1969

RANDRUP, A. and MUNKVAD, I. Roles of brain noradrenaline and dopamine in pharmacologically induced aggressive behaviour. Symposium on Pharmacological Agents and Biogenic Amines in the Central Nervous System. Edited by J. Knoll and K. Magyar. Budapest, Hungary: Akademia Kiado, 1973. Pp. 131-139.

RANDRUP, A., and MUNKVAD, I. Stereotyped behavior. Section 25 of The International Encyclopedia of Pharmacology and Therapeutics (in press)

RANDRUP, A. and MUNKVAD, I. Stereotype behavior produced by amphetamine and other substances. Investigations on the mechanism of action. Neuro-Psychopharmacology, Vol. 5. Edited by H. Brill, J.O. Cole, P. Deniker, H. Hippius and P.B. Bradley. Amsterdam, the Netherlands: Excerpta Medica Foundation, 1967. P. 1224.

Since our report to the fourth C.I.N.P. meeting about amphetamine-induced abnormal, stereotype behavior we have extended our studies of the underlying neural mechanisms.

It was found that rats pretreated with alpha-methyl-p-tyrosine, which inhibits the synthesis of DOPA, remained quiet after amphetamine, and that the stereotype sniffing and biting activity could be restored by 1-DOPA in relatively low dose (100-200 mg/kg s.c.). Stereotype behavior could also be produced in untreated animals by 1-DOPA alone, but then a larger dose was necessary (1200 mg/kg s.c.).

Catecholamines thus seem to play an important role in the mechanism which produces stereotype behavior but neither alpha-nor-beta-adrenergic receptors are involved, since blockade of these receptors does not inhibit the amphetamine response. Possibly dopamine carries this activity.

Besides 1-DOPA other naturally occurring substances (5 HTP, tryptamine and phenylethylamine) could also produce stereotype sniffing and biting activity of rats. Acetylcholine, however, seems to inhibit this form of behavior, since anticholinergic agents (1-hyoscyamine, scopolamine, benzhexol (artane), caramiphen (parpanit, pentaphen) and benactyzine) were found to enhance the amphetamine effect and reproduce stereotype activity, which had vanished about 3 hours after amphetamine.

It is thus indicated that certain disturbances of equilibrium between various monoaminergic mechanisms in the brain result in excitation and stereotypy instead of normal varied activity.

The anatomical location of these monoaminergic mechanisms is now also being studies. For this purpose we use intracerebral micro-injections and electrophysiological methods; the preliminary results of this work will be reported.

RANDRUP, A., MUNDVAD, I., FOG, R. and AYHAN, I.H. Catecholamines in activation stereotypy and level of mood. Catecholamines and Behavior. Edited by A. J. Friedhoff. New York: Plenum Press, 1974.

RANDRUP, A., MUNKVAD, I. and SCHEEL-KFÜGER, J. Mechanisms by which amphetamines produce stereotypy, aggression and other behavioral effects. Proceedings of the Symposia-held at the VIII Congress of the Collegium Internationale Neuro-Psychopharmacologicum, Copenhagen, Denmark, August 14-17, 1972. Edited by T.A. Ban, J.R. Boissier, G. J. Gessa, H. Heimann, L. Hollister, H.E. Lehmann. I. Munkvad, H. Steinberg, F. Sulser, A. Sundwall and 0. Vinar. Amsterdam, the Netherlands: North Holland Publishing Company, 1973.

For abstract, see Section I. Methodology of Drug Research.

REICHMAN. L.B., SHIM, C.S., BADEN, M. and RICHTER, R. Development of tolerance to street heroin in addicted and nonaddicted primates. American Journal of Public Health 63(9): 801-803 (1973)

Protocols of acute and chronic heroin administration to babonns were tested to evaluate the effects of sporadic and continual drug usage on the handling of an acute administration of various doses of street heoin. Animals were observed during initial doses, during repeat dosage after a short lapse of time and during a repeat dosage after a longer period of abstinence. The results indicate that acute challenges with large and varying doses of heroin are well tolerated by the chronically addicted animal. A repeat dose of heroin on the same day as an initial dose showed either no cumulative effect, or much less effect than the first dose. The implications are that one dose of heroin can protect the user from the untoward effects of an inadvertently large dose. This could be a mechanism for protection of the addict against the potentially fatal effects of the large variations in heroin content of the street bags he injects. The study further suggests that many acute reaction deaths are not due to true pharmacologic heroin overdosage, but to other factos, such as the effect of quinine, bacteria, sugars, colloids or an immunologic reaction.

RENAULT, P.F., SHUSTER, C.R., HEINRICH, R. and FREEMAN, D.X. Marihuana: Standardized smoke administration and dose effect curves on heart rate in humans. Science 174: 589-591 (November, 1971)

For abstract, see Section I. Methodology of Drug Research.

RIBLET, L.A. and MITCHELL, C.L. The effect of cervical spinal section on the ability of morphine to elevate the jaw jerk threshold to electrical stimulation of the tooth pulp in cats. The Journal of Pharmacology and Experimental Therapeutics 180: 610-615 (1972)

The tooth pulp was stimulated in normal, full spinal section and hemisectioned preparations with either a single monophasic square wave pulse of 0.5-msec duration or a train of four such pulses at 64 Hz. The effect of morphine (2 mg/kg i.v.) upon the threshold voltages required to elicit the jaw jerk response was different in the three preparations. In animals with intact spinal cords, morphine was effective in elevating the jaw jerk threshold. In contrast, morphine had no effect in animals with full spinal section. In addition, in animals in which the cord was hemisectioned, morphine was less effective against tooth pulp stimulation on the side ipsilateral to the site of hemisection than on the contralateral side. These findings suggest that morphine may exert its effect on tooth pulp thresholds either directly or indirectly through a depressant action upon the caudal portion of the spinal nucleus of the trigeminal nerve.

RICHTER, J.A. and GOLDSTEIN, A. Effects of morphine and levorphanol on brain acetylcholine content in mice. The Journal of Pharmacology and Experimental Therapeutics 175(3): 685-691 (1970)

For abstract, see Section II. Drug Chemistry and Metabolism.

RICHTER, J.A. and GOLDSTEIN, A. The effects of morphine-like compounds on the light responses of the brine shrimp Artemia salina. Psychopharmacologia 17: 327-337 (1970)

Methods for the measurement of the light responses of Artemia nauplii and adults are described. Although no effects of levorphanol were found on the positive phototaxis of nauplii, this compound inhibited and partially reversed the negative phototaxis of adults. Levorphanol was also effective in adults after removal of the compound eyes, indicating that it probably acts on the median eye or its central connections in adults.

Methadone and dextrorphan (the inactive stereoisomer of levorphanol) caused similar effects in adults, but morphine was inactive. Pentobarbital inhibited the negative movement but induced very little positive phototaxis. Attempts to reverse the effect of levorphanol with nalorphine pretreatment were unsuccessful. Attempts to develop tolerance to levorphanol were also unsuccessful; the shrimp died, apparently as a result of an increasing effect of the drug with time.

RICHTER, J.A. and GOLDSTEIN, A. Tolerance to opioid narcotics, II. Cellular tolerance of levorphanol in mouse brain. Proceedings of the National Academy of Sciences 66(3): 944-951 (July, 1970)

For abstract, see Section II. Drug Chemistry and Metabolism.

RINGLE, D.A. and HERNDON, B.L. Binding of morphine by serum proteins of morphine-treated rabbits. Federation Proceedings 32: 2853 (1973)

The possibility that some aspects of tolerance to morphine are immunologic in nature has been considered by a number of investigators. Part of the evidence suggesting an immunologic response to morphine is the occurrence of a humoral factor after treatment with morphine. We have studied the effects of long-term pretreatment with morphine on morphine binding by serum and serum fractions in rabbits. Binding of morphine was measured by Sephadex gel elution and equilibrium dialysis methods using C^{14}-labeled morphine. Results of our investigations on rabbits have demonstrated an increase in morphine binding by sera following morphine treatment with degree of binding related both to length of pretreatment and to method of dosage. Dosage by chronic s.c. pellet implantation of morphine free base was more effective than daily s.c. morphine sulfate injections. Preliminary findings have indicated that the increased binding is associated with the globulin fractions prepared by ammonium sulfate precipitation. The results of these studies suggest that rabbits are capable of responding immunologically to morphine through the production of an immunoglobulin directed against the morphine configuration. Similar studies of this binding phenomenon in other species as well as characterization of the morphine binding component are now in progress.

RINGLE, D.A. and HERNDON, B. L. In vitro morphine binding by sera from morphine-treated rabbits. The Journal of Immunology 109: 174 (1972)

ROCHLIN, M., MILLER, J.W. and SPARBER, S.B. Studies on the central effects of d and l phenoxybenzamine (PBZ). Federation Proceedings 33: 551 (1974)

A comparison was made between the ability of the enantiomers of PBZ to block the uptake of /^{3}H/-7-1-Norepinephrine (^{3}H-NE) by rat brain hypothalamic and striatal slices, as well as inhibit the suggested alpha adrenergically mediated eating response to food satiated animals to intraventricularly administered NE. Whereas both isomers inhibited the uptake of ^{3}H-NE to equal extent in both areas of rat brain (I_{50} ~ 6 x 10^{-5}M), a selective effect of the isomers was noted for blockade of the eating response. Doses of d-PBZ from 0.75 mu-g to 3 mu-g into the lateral ventricle two hours before NE (10 mu-g) inhibited the eating response the following hour in a dose related manner. Three mu-g produced a complete blockade. A dose of 5.5 mu-g of the 1-PBZ inhibited the eating response only to 55% of control eating. Time response studies with d-PBZ (1.0 mu-g) indicated its maximal blocking effect on the eating response occurred two hours after intraventricular administration. The eating response to NE returned within 1 to 2 days after d-PBZ. These data support the contention that alpha-type receptors within the CNS are differentially affected by d and 1 isomers of PBZ in a manner similar to that reported for vas deferens (Miller et al., 1971).

ROEHRS, T. and KHAZAN, N. REM sleep rebound and EEG correlates in methadone dependent rats upon withdrawal. The Pharmacologist 15: 167 (1973)

Rats prepared with chronic electrodes for recording of the EEG and EMG were made dependent on methadone by its administration through chronic indwelling i.v. cannulas. Methadone was administered at an initial dose of 0.15 mg/kg/hr and increased on successive days. reaching 2 mg/kg/hr on the ninth or tenth day. Discontinuation of the injections then precipitated the abstinence syndrome. The primary EEG manifestation of abstinence was a decline in the voltage output of the entire sleep-awake cycle, a phenomenon that correlated with the behavioral hyperirritability of the abstinent rat. The duration of slow wave sleep (SWS) and REM sleep were significantly enhanced within the first six to ten hours after withdrawal. Both SWS and REM sleep then declined to minimal, levels and returned to base-line values by the third day. After this decline, a significant and protracted REM rebound occurred extending up to the twelfth day of abstinence studied. These EEG and behavioral findings provide further evidence of an analogous state of abstinence produced by methadone and morphine.

ROIZIN, L., HELPERN, M., BADEN, M.M., KAUFMAN, M. and AKAI, K. Toxosynpathies (a multifactor pathogenic concept). Drug Abuse: Current Concepts and Research. Edited by W. Keup. Springfield, Illinois: Charles C. Thomas, 1972. Pp. 97-116.

For abstract, see Section II. Drug Chemistry and Metabolism.

ROPPOLO, J.R., WERNER, G., WHITSEL, B.L., DREYER, D.A. and PETRUCELLI, L.M. Phencyclidine action on neural mechanisms of somesthesis. Neuropharmacology 12(5): 417-431 (1973)

The effect of phencyclidine on the activity of neurons in somatic sensory areas I and II was determined in Rhesus monkeys. In the behaviorally significant dose range of 200-300 mu-g/kg, phencyclidine augmented the neural responses to natural, cutaneous stimuli in somatic sensory area II consistently and drastically. With neurons in somatic sensory area I, the phencyclidine effect was in the same dose range variable and inconsistent; but, in almost all instances different from the changes in neural activity which accompany slow wave sleep.

The experimental findings are interpreted as evidence for a relatively specific phencyclidine action on the phylogenetically older and more primitive somesthetic projection system to somatic sensory area II.

ROSCHENTHALER, R., DEVYNCK M.A., FROMAGEOT, P. and SIMON, E.J. Inhibition of the synthesis of 5s ribosomal RNA in E. coli by levallorphan. Biochirnica et Biophysics Acta 182: 481 (1969)

Levallorphan (1. 54. 10^{-3} M) inhibits RNA biosynthesis by 70% whereas the synthesis of protein is inhibited by 14%. The residual synthesis of tRNA under such conditions is greater by at least a factor of 2 than that of high molecular weight RNA. mRNA synthesis, on the contrary, seems to be only slightly inhibited or not at all. Levallorphan therefore exhibits effects similar to levorphanol.

As the origin of 5-S RNA has been the subject of recent discussion we analyzed the extent of its synthesis in the presence of levallorphan. It has been found that 5-S RNA synthesis is inhibited by the drug at least as profoundly as high molecular weight RNA, a result which puts the 5-S RNA in the same class as the ribosomal RNA's and suggests that the same type of control mechanism regulates the synthesis of 5-S, 16-S and 23-S RNA's.

ROSENBERG, H.C. and OKAMOTO, M. Electrophysiology of barbiturate withdrawal in the spinal cord. Federation Proceedings 33: 528 (1974)

Cats were made physically dependent on sodium pentobarbital administered twice daily via intragastric route using the maximally tolerable dosing technique (2nd. Int'l. Symp. Drug Addiction). All animals treated this way exhibited signs of severe dependence, including grand mal type convulsions. At various times after abrupt withdrawal of the drug, electro-physiological measurements of spinal cord activity were made. Under volatile anesthesia, the neuraxis was sectioned at C-l and artificial respiration was begun. The lumbar cord was exposed and peripheral nerves of one hindleg were prepared for stimulation. Action potentials were recorded from ipsilateral L-7 and S-1 ventral roots that had been cut near their exit through the dura mater. Following single, supramaximal stimuli to the sciatic trunk, there was little alteration in the size of the monosynaptic (2-N) response, but the polysynaptic response was increased, and the duration of discharge was increased in abstinent animals as compared to controls. Stimulating specific motor nerves, the rate of recovery of the 2-N synapse was increased. The relationship between 2-N post-tetanic potentiation (PTP) and frequency of conditioning tetanic stimuli was shifted in the direction of lower frequencies. The size of the motor neurone pool, as estimated by maximum PTP, was not changed during abstinence, but the 2-N discharge zone was slightly enlarged.

ROSENBLATT, J.E., JANOWSKY, D.S., DAVIS, J.M. and EL-YOUSEF, M.K. The augmentation of physostigmine toxicity in the rat by delta-9-tetrahydrocannabinol. Research Communications in Chemical Pathology and Pharmacology 3(3): 479-482 (1972)

Sprague-Dawley rats were treated with delta-9-THC (2 mg/kg) and physostigmine salicylate (0.4 mg/kg) or with physostigmine salicylate alone. Seventeen rats received the combined THC-physostigmine treatment; of these animals, 13 died and four survived. Seventeen rats received physostigmine salicylate and propylene-glycol serum complex without THC; of these animals, two died and 15 survived. This difference was highly significant (p is less than .0002). Both atropine and methylscopolamine decreased the lethality of the THC-physostigmine combination. Delta-9-THC appears to augment physostigmine toxicity in the rat.

ROSENCRANS, J.A. and SHEARD, M.H. Effects of an acute stress on forebrain 5-hydroxytryptamine (5-HT) metabolism in C.N.S. lesioned and drug pretreated rats. European Journal of Pharmacology 6: 197 (1969)

C.N.S. lesioned or drug pretreated male albino rats were subjected to a l hr horizontal oscillation stress. An analysis of forebrain 5-HT and 5-HIAA levels indicated that p-CPA pretreatment or M.F.B. lesions facilitated 5-HT turnover in response to stress. Raphe lesions, on the other hand, prevented this latter facilitation of indolamine turnover. The results obtained were explained on the basis of an operative negative feedback system in stressed rats. The lack of a change in raphe lesioned rats, further reinforced the concept that most forebrain 5-HT containing neurons are the result of axons extending from this nucleus.

ROSENFELD, G.C. and BURKS. T.F. Single dose tolerance to morphine hypothermia in rats. Proceedings of the 6th International Congress of Pharmacbiogy, Helsinki, Finland, July 20-25, 1975.

Temperature responses to morphine were studied in outbred (TIMCO, Houston) Sprague-Dawley male rats. Initial subcutaneous injections of morphine (10 mg/kg) produced biphasic changes in rectal temperature: a fall in temperature of approximately 2° C. followed by a small rise of 0.5-1.0° above preinjection temperature. Responses to a second 10 mg/kg dose or morphine depended on the interval of time separating the two injections. When the second morphine injection was given within seven days of the first, the hypothermic component of the response was attenuated and the hyperthermic component was exaggerated. Maximum tolerance to the hypothermic effect of morphine occurred 48-72 hours after the initial dose. A second dose of morphine was fully effective in comparison with the first when the two were separated by 15 days. Qualitatively similar results were obtained in rats maintained on high (300 mg/kg per day) doses of morphine: loss of the hypothermic response and exaggeration of the hypothermic response. In these rats, a single 10 mg/kg dose of morphine did not elicit a fall in temperature until after at least seven days of abstinent withdrawal, after which responsiveness increased. The hypothermic response was fully restored after 30 days of abstinence. Our results indicate that a single small dose of morphine can induce early tolerance which is comparable to that produced by repeated large doses of morphine. The changes in responsiveness caused by the single dose of morphine can persist for several days after which recovery occurs.

ROSENMAN, S.J. and SMITH, C.B. ^{14}C-catecholamine synthesis in mouse brain during morphine withdrawal. Nature 240: 153-155 (1972)

SANDERS-BUSH, E. Recent studies on the mechanism of action of chlorinated amphetamines. Serotonin and Behavior. Edited by J. Barchus and E. Usdin. New York: Academic Press, 19

SANDERS-BUSH, E., BLUMBERG, J.B. and SULSER, F. Biochemical effects of chlorinated amphetamine derivatives. Psychopharmacologia 26(Supplement): 34 (1972)

The administration of p-chloroamphetamine (PCA) to rats causes a number of changes in cerebral biochemistry which are not produced by amphetamine. Among these are marked alterations in the metabolism and release of intraventricularly-administered norepinephrine -H^3, and a simultaneous decrease in the cerebral levels of serotonin (5HT) and its major metabolite, 5-hydroxyindole acetic acid. Recently, by direct examination of cerebral tryptophan hydroxylase, we have found that the administration of PCA and p-chloromethamphetamine to rats causes a pronounced reduction in cerebral tryptophan hydroxylase with no change in the activity of 5-hydroxytryptophan decarboxylase. Since these drugs do not inhibit tryptophan hydroxylase if added in vitro, experiments were designed to study the mechanism of the decrease in enzyme activity which follows their in vivo administration. The in vivo formation of a metabolite of PCA which inhibits tryptophan hydroxylase, does not appear to occur. Our results suggest that PCA may reduce the amount of active enzyme without altering its properties. Following the administration of PCA to rats, the uptake of 5HT-H^3 into a crude suspension of synaptosomes and mitochondria is reduced. Both the enzyme inhibition and the blockade of uptake are extremely long-lasting. Two weeks following the administration of PCA (10 mg/kg, i.p.), the concentration of 5HT and the activity of tryptophan hydroxylase were significantly reduced in all regions of the brain and in

Sanders-Bush, E., Blumherg, J.B. and Sulser, F. Biochemical effects... continued

the spinal cord. The most pronounced reduction was found in the striatum and cerebral cortex. Likewise, the uptake of 5HT-H^3 into crude synaptosomal preparations of specific brain regions was significantly reduced in all areas, with the most pronounced decrease in the cerebral cortex. In contrast to amphetamine, PCA lowers the endogenous level of cyclic AMP in brain; the possible significance of this change in relation to the other effects of PCA will be discussed.

SANDERS-BUSH, E., BUSHING, J. A. and SULSER, F. Long-term effects of p-chloroamphetamine of tryptophan hydroxylase activity and on the levels of 5-hydroxytryptamine and 5-hydroxyindole acetic acid in brain. European Journal of Pharmacology 20: 385-388 (1972)

The i.p. administration of a single dose of 10 mg/kg of p-chloroamphetamine to rats causes a reduction in the activity of cerebral tryptophan hydroxylase and a decrease in levels of 5-hydroxytryptamine and 5-hydroxyindole acetic acid in brain for as long as 4 months after injection. Two weeks after injection, the activity of tryptophan hydroxylase and the level of 5-hydroxytryptamine in brain are reduced by 59 and 53% respectively. The irreversible tryptophan hydroxylase inhibitor, p-chlorophenylalanine, also decreases the brain level of 5-hydroxytryptamine; however, this effect has disappeared 2 weeks after injection.

SANDERS-BUSH, E., BUSHING, J. and SULSER, F. P-chloroamphetamine: Inhibition of cerebral tryptophan hydroxylase. Biochemical Pharmacology 21: 1501-1510 (1972)

Earlier experiments have suggested that the simultaneous decrease in the levels of 5-hydroxytryptamine (5HT) and 5-hydroxyindole acetic acid (5HIAA) in brain following the administration of p-chloroamphetamine and E-chloromethamphetamine may be the consequence of an inhibition of the synthesis of cerebral 5HT. In the present investigations, the effects of these drugs have been examined on the activity of cerebral tryptophan hydroxylase. The addition in vitro of either p-chloroamphetamine or p-chloromethamphetamine does not reduce the activity of tryptophan hydroxylase isolated from brainstems of rats. Under similar conditions, p-chlorophenylalanine causes marked inhibition. However, when tryptophan hydroxylase was assayed in preparations obtained from brains of rats treated 16 hr previously with p-chloroamphetamine, a dose-related reduction in the activity of the enzyme was observed. Experiments involving various combinations of enzyme preparations from control rats and from rats pretreated with p-chloroamphetamine do not indicate the presence of an inhibitor in the preparations isolated from rats pretreated with the drug. Moreover, the reduction in enzyme activity was not removed by dialysis. Kinetic studies showed that the K_m values for tryptophan and $DMPH_4$ were the same for the enzyme isolated from control rats and from rats pretreated with p-chloroamphetamine. The reduction of cerebral 5HT and the decrease in the activity of tryptophan hydroxylase occur simultaneously; both effects are still present 6 days following a single dose of 10 mg/kg of p-chloroamphetamine. It is concluded that the inhibition of cerebral tryptophan hydroxylase by p-chloroamphetamine can satisfactorily explain the prolonged reduction in the levels of 5HT and 5HIAA in brain.

SATTIN, A., RALL, T.W. and ZANELLA, J. Regulation of cyclic AMP levels in guinea pig cerebral cortex by interaction of alpha-adrenergic and adenosine receptor activity. The Journal of Pharmacology and Experimental Therapeutics (in press)

Direct assay of cyclic AMP in guinea pig cerebral cortex in vitro has shown that an alpha-adrenergic receptor that was previously found to increase tissue content of cyclic AMP requires the co-presence of adenosine. This alpha-adrenergic receptor complex was characterized with blocking agents and contrasted with other activities by examining the effect of other biogenic amines on cyclic AMP content in the presence of adenosine. Phentolamine (but not propranolol) reduced the potentiated response to norepinephrine (or epinephrine) + adenosine to the level seen with adenosine alone. Theophylline, an adenosine antagonist, blocked the entire effect of NE + adenosine. The failure of a high Mg^{++}/Ca^{++} ratio to block the effect of NE + adenosine argues against indirect mediation of the alpha-receptor effect via the release of K^{+} or via an unknown neurohumoral agent. The complex variety of potentiative interactions between biogenic amines and adenosine is unique to brain. These interactions may be explained by the proposed existence of both independent and dependent receptors. The dependent receptors respond only to the co-presence of two or more neurohumoral agents. An alternative explanation would involve a compartmentally selective impairment of cyclic AMP degradation.

SCHANBERG, S.M. and COOK, J.D. Effects of acute and chronic methamphetamine on brain norepinephrine metabolism. Current Concepts in Amphetamine Abuse. Edited by E. Ellinwood, Jr. and S. Cohen. Washington, D.C.: U.S. Government Printing Office, 1972.

SCHECHTER, M.D. and WINTER, J.C. Effect of BOL on the LSD induced alteration of flicker discrimination in the rat. Archives internationales de Pharmacodynamie et de Therapie 196(1): 64 (1972)

Rats were trained on a multiple schedule of positive reinforcement. A stimulus light source flickering at 100 cycle/sec provided the discriminative stimulus (S^{d}). Under the S^{d} condition, reinforcement was contingent upon an FR10 schedule. The same light source flickering at 30 cycle/sec constituted the S^{delta} condition. Brom-lysergic acid diethylamide (BOL), at doses of 1 and 3 mu-mol/kg had no effect on discriminative ability, whereas, 10 mu-mol/kg BOL significantly decreased it. A dose of 0.2 mu-mol/kg lysergic acid diethylamide (LSD), which by itself elevated discriminative ability, was shown not to be effected by co-administration of the three doses of BOL. The results indicate that BOL lacks LSD-like effects in this test system and the LSD congener is incapable of antagonizing the LSD-induced alteration of discrimination when co-administered.

SCHECHTER, M.D. and WINTER, J.C. Effect of mescaline and lysergic acid diethylamide on flicker discrimination in the rat. The Journal of Pharmacology and Experimental Therapeutics 177(2): 461 (1971)

Rats were trained on a multiple schedule of positive reinforcement. A stationary light source flickering at 100 cps provided the discriminative stimulus (S^d). In the presence of S^d, reinforcement was contingent upon a fixed ratio 10 schedule. The same light source flickering at either 20 or 30 cps constituted the S^{delta} period. Mescaline, at doses of 40 and 60 mu-mole/kg, produced a significant decrease in discriminative ability, whereas lysergic acid diethylamide (0.2, 0.3 and 0.4 mu-mole/kg) caused a significant increase. A dose of mescaline (20 mu-mol/kg) which by itself had no significant effect on discrimination, significantly reduced the increase caused by lysergic acid diethylamide. Likewise, a subeffective dose of lysergic acid diethylamide (0.1 mu-mol/kg) significantly antagonized the depression of discriminative ability caused by mescaline. These results indicate that flicker discrimination provides a sensitive measure of drug action in the rat. The pharmacologic data suggest that lysergic acid diethylamide and mescaline are mutually antagonistic in this system.

SCHEEL-KRÜGER, J. Behavioural and biochemical comparison of amphetamine derivatives, cocaine, benztropine and tricyclic anti-depressant drugs. European Journal of Pharmacology 18: 63-73 (1972)

The present biochemical studies demonstrate that tricyclic antidepressant drugs, such as desipramine, imipramine and protriptyline, which inhibit the reuptake process in central noradrenaline neurons, and benztropine, which inhibits the reuptake process in central dopamine neurons do not increase the accumulation of O-methylated noradrenaline. normetanephrine, nor-O-methylated dopamine, 3-methoxytyramine in the brain of rats pretreated with a monoamineoxidase inhibitor, nialamide.

The central stimulant drugs, d-amphetamine, l-amphetamine, p-chloroamphetamine and cocaine increased accumulation in the brain of both normetanephrine and 3-methoxytyramine. Furthermore these central stimulants decreased the brain noradrenaline level; the brain dopamine level remained unchanged. Dextroamphetamine and l-amphetamine were equally active on brain noradrenaline metabolism, whereas d-amphetamine was most potent on dopamine metabolism.

These results suggest that the effect on normetanephrine and 3-methoxytyramine in this biochemical test is correlated with catecholamine-releasing properties of the central stimulant drugs and not with an influence on the reuptake mechanism in catecholamine neurons. Comparative behavioral studies in the rats demonstrate similarities between d-amphetamine, l-amphetamine, p-chloroamphetamine and cocaine with respect to development of locomotor and rearing activity as well as stereotyped behaviour. Dextroamphetamine was 10 times more potent than l-amphetamine with respect to locomotor activity and 4-6 times more potent with respect to the development of stereotyped behaviour. Benztropine increased locomotor and rearing activity but produced no stereotyped behaviour.

SCHEEL-KRÜGER, J. Central effects of anticholinergic drugs measured by the apomorphine gnawing test in mice. Acta Pharmacologia et Toxicologia 28: 1-16 (1970)

Apomorphine in doses ranging from 10 up to 60 mg/kg given subcutaneously to mice induced only weak gnawing behaviour and 10 mg/kg was without effect. The addition of anticholinergic drugs given 15 min. before 10 mg/kg apomorphine potentiated the gnawing behaviour. 9 tertiary and 3 quaternary drugs were tested. Among these some quinuclidinylesters, scopolamine and benztropine were found to be very active compared with atropine. The quaternary compounds showed much weaker activity than the corresponding tertiary analogues. The gnawing activity produced by atropine plus apomorphine was only weakly antagonized by the apomorphine antagonistic drug spiramide; physostigmine showed a better inhibitory effect and combined treatment with spiramide and physostigmine gave a pronounced antagonistic effect. Since the apomorphine gnawing behavior is most probably related to an interaction with central dopamine receptors, these findings suggest there is a central counter balancing dopaminergic-cholinergic system.

SCHEEL-KRÜGER, J. Comparative studies of various amphetamine analogues demonstrating different interactions with the metabolism of the catecholamines in the brain. European Journal of Pharmacology 14: 47-59 (1971)

Behavioural studies on the effects of amphetamine, methamphetamine, phenmetrazine, pipradol, NCA and methylphenidate administered to rats pretreated with reserpine or alphamethyltyrosine and additional biochemical analyses demonstrated that all six stimulants affected both brain dopamine and brain noradrenaline metabolism.

The present study permits a distinct separation of these drugs into two groups since the interaction with the catecholamines was found to be mediated by two different mechanism of action: behaviourally, excitation, consisting of locomotor and stereotyped activities after amphetamine, methamphetamine and phenmetrazine, was virtually impossible to inhibit with reserpine even in extremely high doses (50 mg/kg), but was, in contrast, strongly inhibited by alpha-methyltyrosine. Biochemically, the excitation in reserpinized rats was correlated with the metabolic influence on a reserpine-resistant pool of dopamine.

The very similar behavioural effects produced by pipradrol, NCA, and methylphenidate were in sharp contrast found to be correlated with the influence on a reserpine-resistant pool of the catecholarnines and not with the newly synthesized catecholamines.

Reserpine completely inhibited all behavioural and biochemical effects of pipradrol, NCA and methylphenidate.

SCHEEL-KRYÜGER, J. On the possible interrelationship in mechanism of action between morphine, amphetamine and neuroleptic drugs. Frontiers in Catecholamine Research. Edited by E. Usdin and S.H. Snyder. New York: Pergamon Press, 1973. Pp. 1027-1029.

SCHEEL-KRÜGER. J. Pharmacological studies on a counter -balancing adrenergic - cholinergic system in the brain. Acta Physiologica Scandinavica 330 (Supplement): 66 (1969)

Previous papers have described the behavioural excitation with increased locomotion and stereotyped behaviour induced by amphetamine or apomorphine in rats and mice. Particularly, the stereotyped behaviour seems produced by activating a doparninergic mechanism in corpus striatum.

The results of this paper show that a cholinergic system exists, which shows antagonism against this adrenergically provoked behaviour, since the stereotypy is potentiated and prolonged by anticholinergica (atropine, scopolamine) and weakly antagonized by cholinergica (physostigimine, oxotremorine). Among the characteristic actions for neuroleptica are the antagonism of amphetamine or apomorphine induced stereotyped behaviour and development of catalepsy, which actions are probably produced by blockage of adrenergic (dopaminergic?) mechanisms in brain. Results of combined drug treatments of nenrolcptica and anticholinergica or cholinergica show that the inhibitory activity of a cholinergic system also contributes to the development of these characteristic actions of neuroleptica.

It is concluded that a counterbalancing adrenergic-cholinergic system exists in brain, which involves behavioral features as locomotor activity and stereotyped behavior.

SCHEEL-KRÜGER, J. Some aspects of the mechanism of action of various stimulant amphetamine analogues. Psychiatria, Neurologia, Neurochirurgia 75: 179-192 (1972)

In the present paper the available evidence on the possible mechanisms of action of amphetamine and various amphetamine derivatives is discussed. The conclusion is that the central stimulant effects of these drugs are mainly correlated with catecholamine-releasing properties, while the inhibitory influence of these drugs on the reuptake mechanisms in dopamine and noradrenaline neurons is considered of secondary importance.

It is discussed that the moderate influence of amphetamine and other beta-phenylisopropylamines on monoamine-oxidase is not related to the central potency of these drugs. This effect seems mainly indirectly related to the effect of these drugs on the release and the re-uptake mechanisms but is also of importance for the protection of these drugs against a rapid inactivation and metabolism via oxidative deamination.

Finally evidence is presented, which allows a separation of various amphetamine derivatives into two groups due to the interaction with two different intraneuronal pools of the brain dopamine (and noradrenaline?).

SCHEEL-KRÜGER, J. Studies of various amphetamines, apomorphine and clonidine on body temperature and brain 5-hydroxytryptamine metabolism in rats. Psychopharmacologia 36: 189-202 (1974)

For abstract, see Section II. Drug Chemistry and Metabolism.

SCHEEL-KRÜGER, J. Studies on the accumulation of O-methylated dopamine and noradrenaline in the rat brain following various neuroleptics, thymoleptics and aceperone. Archives internationales de Pharmacodynamie et de Therapie 195: 372-377 (1972)

The influence of some neuroleptic drugs (chlorpromazine, chlorprothixene. pimozide, spiramide), thymoleptic drugs (desipramine, imipramine) and the noradrenaline blocking drug aceperone on the accumulation of brain normetanephrine and 3-methoxytyramine was studied in rats pretreated with a monoamine oxidase inhibitor, pargyline. The results demonstrate that the neuroleptic drugs in common produced a highly significant increase of O-methylated dopamine, 3-methoxytyramine, while the other drugs did not produce alteration on this metabolite. Chlorpromazine and chlorprothixene in a 10 mg/kg dose produced furthermore the largest increase of O-methylated noradrenaline, normetanephrine (2.0 and 1.8 times the control value, respectively). Spiramide (5 mg/kg) and pimozide in various doses (1; 5 and 10 mg/kg) in common produced a small but signigicant increase of normetanephrine (1.4 times the control), whereas aceperone (10 mg/kg) and imipramine (50 mg/kg) produced an even smaller (1.3 times the control) but still significant increase of normetanephrine. None of the used drugs produced large changes on the brain dopamine and noradrenaline levels.

SCHEEL-KRÜGER, J., BRAESTRUP, C., EPLOV, L. and NIELSEN, M. The effect of amphetamine and reserpine on 3H-noradrenaline and its metabolites synthesized from intraventricular injected 3H-dopamine. Acta Pharmacologica et Toxicologica 35(Supplement I): 50 (1974)

For abstract, see Section II. Drug Chemistry and Metabolism.

SCHEEL-KRÜGER, J., EPLOV, L. and NIELSEN, M. The effect of protriptyline on the metabolism of labelled dopamine and noradrenaline in the rat brain. Psychopharmacologia 26(Supplement): 45 (1972)

For abstract, see Section II. Drug Chemistry and Metabolism.

SCHEEL-KRÜGER, J. and HASSELAGER. E. Studies of various amphetamines, apomorphine and clonidine on body temperature and brain 5-hydroxytryptamine metabolism in rats. Psychopharmacologia 36: 189-202 (1974)

Amphetamine and various amphetamine derivatives, phenmetrazine, pipradrol. methylphenidate and NCA can increase the concentration of 5-HIAA in the rat brain without changing that of 5-HT. Metamphetamine produced a decrease in 5-HT and no effect on 5-HIAA whereas p-hydroxyamphetamine produced no effects on 5-HT and 5-HIAA. The experiments performed at different environmental temperatures (12-14°C, 21-22°C and 21-28°C) with simultaneous measurements of the body temperature indicate that no simple correlation exists between the drug induced hyperthermia and the effect on 5-HIAA. The amphetamine and phenmetrazine effect on 5-HIAA seems to be related to hyperthermia whereas the pipradrol and methylphenidate effect on 5-HIAA appears independent of hyperthermia. Apomorphine (2 x 2.5 mg/kg) which activates central dopamine receptors produced a significant increase in 5-HIAA whereas clonidine (0. 5 mg/kg) which activates central noradrenaline receptors produced a significant decrease in 5-HIAA.

In conclusion, the effect of various amphetamines on 5-HT metabolism seems very complex in mechanism of action and might be related to hyperthermia, to a direct effect on 5-HT neurons and to the ratio between central dopamine/noradrenaline receptor activation of these drugs.

SCHBEL-KRÜGER, J. and JONAS, W. Pharmacological studies on tetrabenazine induced excited behaviour of rats pretreated with amphetamine or nialamide. Archives internationales de Pharmacodynamie et de Therapie 206(1): 47-65 (November, 1973)

Tetrabenazine (50 mg/kg) injected 1½ after various doses of amphetamine (0.25-10 mg/kg) produced a 5-10 times potentiation of the amphetamine-induced gross behavioural effects in rats: locomotion, rearing and stereotyped activities. However, the amphetamine-tetrabenazine excitation was shortlasting. 6-36 min dependent on the amphetamine dose. Tetrabenazine (50 mg/kg) injected after cessation of the amphetamine excitation (i. e. 4½ h after 5 mg/kg amphetamine) was also able to reinduce a shortlasting and typical amphetamine-like stimulation lasting 12-18 min. Neuroleptic drugs with dopamine receptor blocking properties haloperidol, perphenazine and spiramide produced in very small doses complete inhibition of all behavioural effects in the amphetamine-tetrabenazine reversal test, whereas noradrenaline receptor blocking drugs aceperone and phenoxybenzamine in very high doses only produced partial inhibition of the locomotor and rearing activities. Scopolamine increased the tetrabenazine reversal effect. A single, relatively low, dose of alpha-methyltyrosine (100 mg/kg) produced no inhibition of the amphetamine-tetrabenazine excitation, whereas high repeated doses of alpha-methyltyrosine (2 x 350 mg/kg) or reserpine (7.5 mg/kg) produced complete inhibition of the amphetamine-tetrabenazine excitation. The present studies indicate that the strong potentiation effect of tetrabenazine in amphetamine pretreated rats is dependent on a tetrabenazine-induced release of the catecholamines from a reserpine sensitive storage pool to an extragranular pool available for amphetamine release. The excitation produced by nialamide-tetrabenazine was found very longlasting but not as strong and intense in appearance as after amphetamine. The nialamide-tetrabenazine excitation was potentiated by scopolamine, completely antagonized by the dopamine antagonist spiramide and partially antagonized by the noradrenaline antagonists, aceperone and phenoxybenzamine.

SCHEEL-KRÜGER, J. and RANDRUP, A. Evidence for a cholinergic mechanism in brain involved in the tetrabenazine reversal by thymoleptic drugs. Journal of Pharmacy and Pharmacology 21: 403-406 (1969)

SCHEEL-KRÜGER, J. and RANDRUP, A. Pharmacological evidence for a cholinergic mechanism in brain involved in a special stereotyped behaviour of reserpinized rats. British Journal of Pharmacology 34(1): 217 (1968)

SCHEEL-KRÜGER, J. and RANDRUP, A. Production of a stereotyped behaviour in rats by dopamine in the absence of noradrenaline. Acta Pharmacologia et Toxicologia 25 (4): 61 (1967)

Randrup, Munkvad and Usdin (1963) and Randrup and Munkvad (1967) have described the stereotyped behaviour induced in many species of animals by amphetamine. The same form of a stereotype behaviour can be produced in rats after injection of 1-DOPA, the physiological precursor of dopamine and noradrenaline (Randrup and Munkvad, 1966).

In this paper the various forms of experiments are presented, which have been done to obtain a differentiation between the behavioural effects induced by dopamine and noradrenaline.

Scheel-Kruger, J. and Randrup, A. Production of a stereotyped. . . continued

Biochemical analyses have been made of these brain amines and their 3-o-methylated metabolites, 3-methoxytyramine and normetanephrine (Scheel-Krüger and Randrup, 1967).

Analyses were made at various times after 1-DOPA, of the brain amines from rats pretreated with either a monoamine inhibitor (MAOI) pargyline or of rats first depleted of catecholamines by reserpine and then treated with nialamide (a MAOI) + 1-Dopa.

The best differentiation between the behavioural effects of noradrenaline and dopamine was however obtained, when diethyldithiocarbamate DDC was added to the treatment. DDC blocks the biosynthesis of noradrenaline from injected DOPA but not that of dopamine (Goldstein, 1966).

These analyses together with other results show that a continuous stereotype behaviour induced after injection of 1-DOPA to rats is dependent on a high level of dopamine.

Furthermore it is shown that this behaviour is independent of the levels and turnover of noradrenaline.

SCBEEL-KRÜGER, J. and RANDRUP, A. Stereotyped hyperactive behaviour produced by dopamine in the absence of noradrenaline. Life Sciences 6: 1389 (1967)

Two phases of behavioural excitation result from injection of DOPA (physiological precursor of dopamine and noradrenaline) into rats pretreated with a monoamine-oxidase (MAO) inhibitor. The first phase, starting 20 to 35 min. after the injection, is characterized by rage: hissing and spitting, some rapid movements, fighting if animals were put together. During this period the head is kept elevated in a characteristic fashion, and there is no sniffing.

1 to 2 hrs. after the injection there is a gradual transition into the second phase, where the behaviour is completely different, characterized by continuous stereotype sniffing, licking or biting of the cage wire netting. This behaviour is similar to that elicited by medium doses of amphetamine or apomorphine.

Since it is generally agreed that the behavioural excitation produced by DOPA is due to the formation of the catecholamines dopamine and noradrenaline in the brain, we thought that determination of these brain amines might help to explain the behavioural observations. In the following we present the results obtained by this approach.

SCBELLING, J-L. and LASAGNA, L. A study of cross-tolerance to circulatory effects of organic nitrates. Clinical Pharmacology and Therapeutics 8: 256-260 (1967)

Ten hospitalized volunteer subjects were given pentaerythrol tetranitrate ‘(PETN) daily in divided doses over a period of four weeks. Before and during PETN treatment, the subjects were challenged with 0.3 mg sublingual nitroglycerin (NTG). The changes in blood pressure and heart rate after NTG were significantly decreased while subjects were receiving PETN. Reports of NTG- and PETN-related headache also decreased during PETN administration. Since long-acting nitrates may carry within them the seeds of their own therapeutic failure via the development of tolerance, it is suggested that animal studies on such agents routinely include repeated pharmacological testing designed to detect and measure the development of tolerance to cardiovascular and other effects.

SCHLANT, R.C. and NUTTER, D.O. Effect of lysergic acid diethylamide (LSD) upon ventricular function and myocardial contractility. Clinical Research 18: 72 (1970)

The effects of intravenous lysergic acid diethylamide (LSD) upon ventricular function and myocardial contractility have been studied in a total of 8 open chest dogs anesthetized with chloralose (total 114 mg/kg i.v.) and morphine (0.7 mg/kg i. m.). Dose response curves were obtained following the intravenous injection of cumulative doses of LSD ranging from 0.1 to 160 mu-g/kg. Insignificant changes were noted at cumulative doses less than 40 mu-g/kg; however, cumulative doses of 40, 80 and 160 mu-g/kg resulted in progressive, marked depression of left ventricular (LV) function and myocardial contractility. A cumulative dose of 80 mu-g/kg in 3 dogs resulted in the following average changes from control values: LV systolic pressure -14.4%, LV end-diastolic pressure +17.1%, LV max dp/dt -25.4% (Telco micromanometer); LV end-diastolic internal diameter +7.7% (sonomicrometer); peak LV isometric tension -28.4%, max rate of tension development -32.7% (Brodie-Walton guage); LV stroke output -24.4% and peak aortic flow rate -16.2% (electromagnetic flow meter). Heart rate decreased an average of 31 beats/mm and transient A-V dissociation occurred in 1 dog. Average aortic diastolic pressure decreased by 16.1%. The administration of intravenous LSD in moderate dosage in the anesthetized dog produces marked depression of LV function and contractility together with moderate bradycardia.

SCHUBERT, J., FYRO, B., NYBACK, H. and SEDVALL, G. Effects of cocaine and amphetamine on the metabolism of tryptophan and 5-hydroxytryptamine in mouse brain in vivo. Journal of Pharmacy and Pharmacology 22(11): 860-862 (November, 1970)

SCHUBERT, J., NYBACK, H. and SEDVALL, G. Accumulation and disappearance of ^{3}H-tryptophan in mouse brain; effect of LSD-25. European Journal of Pharmacology 10: 215-224 (1970)

For abstract, see Section 1. Methodology of Drug Research.

SCHUBERT, J., NYBACK, H. and SEDVALL, G. Effects of antidepressant drugs on accumulation and disappearance of monoamines formed in vivo from labelled precursors in mouse brain. Journal of Pharmacy and Pharmacology 22: 136-139 (1970)

SCHUBERT, J., NYBACK, H. and SEDVALL, G. Regional differences in synthesis and turnover of 5-hydroxy-tryptamine formed in vivo from ^{3}H-tryptophan in rat brain. College of International Neuropsychopharmacology. Prag, Czechoslovakia, 1970. P. 391.

For abstract, see Section I. Methodology of Drug Research.

SCHULZ, R., CARTWRIGHT, C. and GOLDSTEIN, A. Reversibility of morphine tolerance and dependence in guinea pig brain and myenteric plexus. Nature 251(5473): 329-331 (1974)

SCHULZ, R. and GOLDSTEIN, A. The effect of catecholamines, acetylcholine and serotonin on the morphine tolerant longitudinal muscle strip of the guinea pig ileum. Federation Proceedings 32: 688 (1973)

Electrically stimulated morphine tolerant muscle strips display reduced sensitivity to catecholamines. The required epinephrine concentration for a 50% twitch inhibition is about 5 times higher (1.1×10^{-7} M) than in controls. The dose-response curve observed for isoproterenol showed a similar shift to the right, producing a maximal depression of only 3% (3×10^{-6} Ml. The greatest loss of sensitivity was seen for dopamine. The ED50 in controls required a concentration of 5.8×10^{-6} M, but in the morphine tolerant state the maximal depression was only about 25% at 1.2×10^{-4}M. The response of the unstimulated strip to acetylcholine was not different in controls or tolerant preparations (ED50 4×10^{-10}M). On the other hand, the tolerant strip exhibits a 10 times higher sensitivity to serotonin (ED50 5×10^{-8} M). Naloxone (225 nM) did not block or reverse the effects of the test compounds, The supersensitivity to serotonin could be caused by a feedback mechanism in the excitatory pathway of the myenteric plexus, and it could account for the morphine tolerance. In this system, a catecholamine may act as an inhibitory modulator of neurotransmission.

SCHULZ, R. and GOLDSTEIN, A. Inactivity of narcotic glucuronides as analgesics and on guinea pig ileum. The Journal of Pharmacology and Experimental Therapeutics 183(2): 404 (1972)

The effects of morphine, levorphanol, morphine -3-glucuronide and levorphanol-3-glucuronide in the electrically stimulated longitudinal muscle strip of the guinea-pig ileum as well as the analgesic action of intracerebrally injected levorphanol and levorphanol-3-glucuronide in mice have been studied. Morphine-3-glucuronide and levorphanol-3-glucuronide did not influence the tension of the electrically stimulated muscle strip. After hydrolysis, twitch inhibition was the same as with morphine and levorphanol standards. Intracerebral injections of 113 pmol (48.9 ng) of doubly labeled ^{3}H-levorphanol-3-^{14}C-glucuronide produced analgesia in mice. Detailed investigations of the mouse brain have shown ^{3}H radioactivity (levorphanol) not to be bound to glucuronic acid. It was demonstrated that intracerebral injection of comparable small amounts of levorphanol could produce analgesia. These results support the conclusion that analgesia seen after intracerebral injection of levorphanol-3-glucuronide is acused by the free base resulting from hydrolysis in vivo.

SCHULZ, R. and GOLDSTEIN, A. Morphine tolerance and supersensitivity to 5-hydroxytryptamine in the myenteric plexus of the guinea pig. Nature 224(5412): 168-170 (July, 1973)

SCHULZ, R. and GOLDSTEIN, A. Morphine tolerance in the longitudinal muscle strip of the guinea pig ileum. Abstracts of Volunteer Papers, Fifth International Congress on Pharmacology, San Francisco, California, 1972.

SCHULZ, R. and GOLDSTEIN, A. Morphine tolerant longitudinal muscle strip from guinea pig ileum. British Journal of Pharmacology 48: 655 (1973)

SCHUSTER, C.R. and VILLARREAL, J.E. The experimental analysis of opioid dependence. Psychopharmacology: A Review of Progress, 1957-1967. Edited by D. Efron, J. Cole, J. Levine and J.R. Wittenborn. Washington, D.C.: U.S. Government Printing Office, 1968. Pp. 811-828.

SCHWARTZ, A.S. and MARCHOK, P.L. Depression of morphine-seeking behaviour by dopamine inhibition. Nature 248(5445): 257 (March, 1974)

SCHWARTZ, A.S. and MARCHOK, P.L. Depression of morphine-seeking behavior in the rat by haloperidol. Committee on the Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council, 1974.

SCHWARTZ, J., FELDSTEIN, S., FINK, M., SHAPIRO, D.M. and ITIL, T.M. Evidence for a characteristic EEG frequency response to thiopental. Electroencephalography and Clinical Neurophysiology 31: 149-153 (1971)

SCHWEITZER, J.W. and FRIEDHOFF, A.J. Enzymatic (brain) formation of mescaline from 4-hydroxy-3, 5-dimethoxyphenethyl-amine. Transactions of American Society of Neurochemistry 3: 1, 119 (1972)

SCRAFANI, J.T., WILLIAMS, N. and CLOUET, D.H. The subcellular distribution of narcotic analgesics in rat brain. Committee on Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council, 1970, P. 7030.

SEEGAL, R.F. and ISAAC, W. Sensory influences upon amphetamine tolerance. Physiology and Behavior 7: 877-879 (1971)

The effects of illumination, noise, and d-amphetamine upon locomotor activity were studied in the rat. While both noise and illumination altered activity level, only illumination was related to the drug effects. The effectiveness of the drug was found to decrease, primarily in the dark, over repeated trials.

SEEVERS, M.H., DAVIS, V.E. and WALSH, M.J. Morphine and ethanol physical dependence: A critique of a hypothesis. Science 170: 1113 (1970)

SEEVERS, M.H. and DENEAU, G.A. A critique of the "dual action" hypothesis of morphine physical dependence. Research Publications of the Association for Research in Mental Diseases 46: 199 (1968)

Newer observations suggest that the hypothesis of dual action can no longer be considered as the sole explanation of morphine addiction. For example, prolonged morphine administration does not result in physical dependence when covered by an antagonist. It is suggested that the development of physical dependence requires reasonably prolonged occupation by morphine-like narcotic analgesics of those receptor sites which induce depression.

SEGAL, D.S. and KUCZENSKI, R. Tyrosine hydroxylase activity: Regional and subcellular distribution in brain. Brain Research 68: 261-266 (1974)

The ratio of soluble to membrane-bound tyrosine hydroxylase activity was determined in the cell bodies and nerve endings of the nigro-striatal pathway (substantia nigra and caudate-putamen, respectively) and of the dorsal NE pathway (locus coeruleus and hippocampus-cortex, respectively) as well as in the hypothalamus which contains both CA cell bodies and nerve endings. Regional dissection was accomplished by a new procedure which allows for the rapid and consistent dissection of discrete brain areas.

The cell body and nerve ending regions obtained by this procedure were found to be distinguishable with respect to subcellular distribution of tyrosine hydroxylase activity independent of the absolute amount of tyrosine hydroxylase. Locus coeruleus and substantia nigra showed a significantly greater proportion of soluble to membrane-bound tyrosine hydroxylase activity than did the caudate-putamen and hippocampus-cortex, where nerve endings predominate. The ratio for the hypothalamus is consistent with the presence of both CA cell bodies and nerve endings in this region. The necessity to distinguish between relatively discrete cell body and nerve ending regions as well as between NE and DA pathways is discussed as a prerequisite for the adequate characterization of the effects of experimental manipulations.

SEGAL, D.S., KUCZENSKI, R. and MANDELL, A.J. Theoretical implications of drug-induced adaptive regulation for a biogenic amine hypothesis of affective disorder. Biological Psychiatry 9(2): 147-159 (1974)

For abstract, see Section II. Drug Chemistry and Metabolism.

SEGAL, D.S., McALLISTER, C. and GEYER, M.A. Ventricular infusion of norepinephrine and amphetamine: Direct versus indirect action. Pharmacology Biochemistry and Behavior 2: 79-86 (1974)

The behavioral hyperactivity produced by intraventricular infusions of norepinephrine in rats is potentiated by pretreatment with 6-hydroxydopamine. Pretreatment with the catecholamine uptake blocker desmethylimipramine does not alter the effect of norepinephrine, which indicates that the potentiation observed after 6-hydroxdopamine is due to an enhancement of receptor sensitivity rather than to a loss of an uptake inactivation mechanism. Intraventricular infusions of d-amphetamine result in behavioral effects which are comparable to those observed following systemically administered amphetamine: (1) increasing doses produce a graded increase in locomotor activity; (2) high doses elicit a pattern of stereotypy; and (3) d-amphetamine is more potent than l-amphetamine in producing these behavioral effects. The behavioral effects of amphetamine, in contrast to those induced by norepinephrine, appear to be dependent upon the functional levels of brain catecholamines as indicated by the suppression of amphetamine effects following pretreatment with alpha-methyl-p-tyrosine or reserpine. These results provide evidence for a direct mechanism of action for infused norepinephrine and indicate the potential usefulness of norepinephrine-induced activity as an index of alterations in receptor sensitivity.

SETHY, V.H. and WINTER, J.C. Effect of chronic treatment with mescaline upon tissue levels of the drug. Experimentia 29: 571 (1972)

SETHY, V.H. and WINTER, J.C. Effects of yohimbine and mescaline on punished behavior in the rat. Psychopharmacologia 23: 160-166 (1972)

This investigation tested the hypothesis that conditioned aversive stimuli and drugs such as yohimbine and mescaline produce a common state in animals. Rats were trained to press a bar on a multiple schedule of reinforcement in which one component was variable interval 30 sec (food) and the other component was fixed ratio 10 (concurrent food and electric shock). Yohimbine did not have a selective depressant effect on response rate during the punished component. Indeed, punished rates were elevated or near normaI when responding in the nonpunished component was decreased to less than 50% of control values. In contrast, mescaline concurrently depressed rates on both components of the schedule. If yohimbine produces an anxiety-like state in animals which is akin to the state engendered by punishment procedures, the effects of punishment and yohimbine should be additive in terms of their depressant effects on lever-press responses. No such additivity was observed in this investigation. The present data do not support the assumption that punishment procedures and the administration of yohimbine produce a common state in the rat. No definitive conclusion could be drawn with respect to the actions of mescaline.

SHAGASS, C. Effects of LSD on somatosensory and visual evoked responses and on the EEG in man. Recent Advances in Biological Psychiatry 9: 209 (1967)

SHAGASS, C. Effects of psychotropic drugs on human evoked potentials. Evoked Potential Findings. Edited by T.M. Itil. Modern Problems in Pharmacopsychiatry, Vol. 8. New York: S. Karger, 1974.

During the past decade, the technique of extracting potentials evoked by sensory stimuli from the scalp EEG by averaging has become almost commonplace. A brief review of the effects of psychotropic agents on sensory evoked activities will be presented here. Other event-related potentials are often considered within the context of evoked potentials: examples are the motor potentials and contingent negative variation (CNV). Only the CNV has received much attention with respect to drug effects; the CNV will be dealt with elsewhere in this volume.

SHAGASS, C. Invited discussion of Drs. M. Fink and T. Itil's paper: Evoked response and behavioral effects of LSD and ditran. Pharmacology: A Review of Progress 1957-1967. Edited by D.H. Efron. Washington, D.C.: PHS Publication No. 1836, 1969.

SHAGASS, C., OVERTON, D.A. and STRAUMANIS, J.J., JR. Evoked response findings in psychiatric illness related to drug abuse. Biological Psychiatry 3: 259-272 (1971)

Possible neurophysiological correlates of psychotic reactions associated with drug abuse were explored by means of a cerebral evoked response test. Median nerve shocks of varying intensity were applied as single conditioning stimuli, or trains, preceding a test shock of fixed intensity. Test response amplitudes were generally lower in 10 drug-abuse patients with a history of psychotic reactions than in 20 nonpatients or in 9 drug-abuse patients without psychotic reactions. Additional data were obtained for 9 male schizophrenics and 5 male nonpsychotic patients without a drug abuse history. Comparing male subjects only, test response amplitudes of groups composed of 8 psychotic drug abusers, 9 schizophrenics, and 5 nonpsychotic patients without drug abuse history were not different from one another, but they differed significantly from those of 15 nonpatients and 6 nonpsychotic drug abusers. Not only were test response amplitudes lower in the former three male groups than in the latter two, but they showed less variation as a function of conditioning stimulus intensity. This relative lack of variation, taken together with lower amplitudes, was interpreted as evidence of a generalized restriction of the level of cortical responsiveness to external stimuli. Such restriction appears to be associated with severe states of emotional disturbance, whether or not they were precipitated by drugs.

SHAGASS, C. and STRAUMANIS, J.J. Evoked potentials and psychopathology. Neurobiological Aspects of Psychopathology. Edited by J. Zubin and C.Shagass. New York: Grune and Stratton, Inc., 1969. Pp. 22-51.

SHANI, A. and MECHOULAM, R. A new type of cannabinoid. Synthesis of Cannabielsoic Acid A by a novel photo-oxidative cyclisation. Chemical Communications, 1970. London, England: The Chemical Society, 1970. P. 273.

For abstract, see Section II. Drug Chemistry and Metabolism.

SHANI, A. and MECHOULAM, R. Photochemical reactions of cannabidiol. Cyclization to delta-1-THC and other transformations. Tetrahedron Letters 27: 601 (1971)

For abstract, see Section II. Drug Chemistry and Metabolism.

SHARPE, L.G., GARNETT, J.E. and CICERO, T.J. Analgesia and hyperreactivity produced by intracranial microinjections of morphine into the preiaqueductal gray matter of the rat. Behavioral Biology 11(3): 303-313 (1974)

Produced by intracranial microinjection of morphine, 137 such injections of morphine sulfate in doses of 1.0-50 mcgs were made into various midbrain sites of 46 rats implanted with chronic indwelling cannulae. Three to 6 mcgs of morphine injected in a 0. 5 mcl volume produced a marked increase in hot plate reaction time when injected into a circumscribed region of the periaqueductal gray matter ventral to the cerebral aqueduct encompassing the dorsal raphe nucleus and bordering tissue. Higher doses of morphine eliminated the pain response to limb pinching, but in addition caused rats to become hyperreactive. The results of these studies are seen to be in agreement with those studies that showed identical sites of action for electrical analgesia in the rat. It is suggested that morphine and electrical stimulation have similar mechanisms of action in producing analgesia when these active midbrain sites are involved.

SHEARD, M.H. Aggressive behavior: Modification by amphetamine, p-chlorophenylalanine and lithium in rats. Agressologie 14(5): 323-326 (1973)

Male rats were habituated to home cages and then exposed to intruder male rats treated with either saline, d-amphetamine, p-chlorophenylalanine, or raphe lesions. There was a significant increase in the aggression of the home cage rat towards intruder rats given the drugs or with lesions. Lithium treatment of home cage rats abolished the aggression.

SHEARD, M.H. The effect of p-chloroamphetamine on single raphe neurons. Advances in Biochemical Psychopharmacology Vol. 10. Edited by E. Costa, G.L. Gessa and M. Sandler. New York: Raven Press, 1974. Pp. 179-184.

An observation of interest during these acute experiments was the fact that with the intravenous injection of PCA there was often an increase in temperature. Previous studies have suggested a relationship between the activity of 5-HT neurons and temperature control. For example, there are increases in 5-HIAA due to hyperthermia (Reid, Volicer, Smookler, Beaven, and Brodie, 1968; Weiss and Aghajanian, 1971). Treatment with PCPA results in a drop in temperature of approximately half a degree. On the other hand, treatment with PCA results in a marked rise in temperature of 1 to 2° C.

In view of the marked motor activity seen in the PCA-treated rats, which is probably related to catecholamine metabolic effects (e.g., increased turnover rate of striatal dopamine; Costa, Naimzada, and Revuelta, 1971b). it appears at first sight that this temperature increase may also be related to catecholamine release and motor activity. However, following pretreatment with AMPT (100 mg/kg, i.p.), which blocks the synthesis of NE, there is an even greater rise in temperature following treatment with PCA, whereas pretreatment with PCPA blocks the rise of temperature.

These findings raise interesting questions with regard to the relationship between 5-HT neuron activity, the control of temperature, and depression.

SHEARD, M.H. The effect of p-chlorophenylalanine on behavior in rats:, Relation to brain serotonin and 5-hydroxyindoleacetic acid. Brain Research 15: 524-528 (1969)

Investigations into the role of serotonin (5-HT) in brain have been considerably advanced by the introduction of p-chlorophenylalanine (PCPA), a drug which inhibits 5-HT synthesis through inhibition of tryptophan hydroxylase in vitro. The most striking behavioral consequences of this chemical depletion of brain serotonin are: a severe impairment in sleep; the development of muricide tendencies in domestic rats; reduction of aggressive behavior in mice; and the development of excessive sexual activity in cats. The experiment reported here was performed in order to clarify further the relationship between these behavioral changes and the brain concentrations of 5-HT and 5-dydroxyindoleacetic acid (5-HIAA).

SHEARD, M.H. and AGHAJANIAN, G.K. Neuronally activated metabolism of brain serotonin: Effect of lithium. Life Sciences 9(1): 285 (1970)

SHEARD, M.H., ZOLOVICK, A. and AGHAJANLAN, G.K. Raphe neurons: Effect of tricyclic antidepressant drugs. Brain Research 43: 690-694 (1972)

These results indicate that the tricyclic antidepressants IMI, AMI and CMI, like the MAO inhibitors, have a significant depressant effect on the firing rate of 5-HT containing neurons in the brain. The findings confirm the recent report that imipramine depresses unit activity of the midbrain raphe of rats. This effect of the tertiary amines on the physiology of 5-HT neurons fits well with their effect on uptake of 5-HT in biochemical studies. These studies also showed that the tertiary amines were much more potent than secondary amines in their effect on 5-HT uptake. It is interesting in this regard also that clinicians prefer to use the tertiary amines over the secondary amines for treating depression. These findings also lend weight to the idea that the mechanism explaining the phenomenon of depressed firing rate of 5-HT neurons seen with both MAO inhibitors and tertiary amine antidepressants may be due to a negative feedback. The feedback is postulated to result from the accumulation of 5-HT at the synapse secondary either to MAO inhibition on the one hand or to a block in the reuptake of 5-HT with the tricyclic compounds on the other. In contrast, the tricyclic compound chlorpromazine, which does not block reuptake of 5-HT, does not modify the firing rate of raphe units. It is suggested that this method of monitoring raphe unit firing rates may be useful in the assessment of potential antidepressant drugs.

SHERMAN, A. and MITCHELL, C.L. Blood citric acid cycle and individual response to morphine analgesia in rats. Experientia 29:176 (1973)

The effect of morphine on glycolytic intermediaries has been studied by numerous investigators. The significant effects on glycolytic intermediaries suggest the possibility of a correlation between glycolytic activity and analgesia. The purpose of this study was to determine whether existing blood levels of citric acid cycle intermediaries were related to the effectiveness of morphine as an analgesic.

Two studies were performed, one to determine whether a relationship between blood levels and individual, response to morphine existed, and the second to determine whether this relationship was due to differential uptake of morphine or to biochemical factors.

SHERMAN, A.D. and MITCHELL, C.L. Effect of morphine on regional levels of gamma-hydroxybutyrate in mouse brain. Neuropharmacology 13: 239-243 (1974)

Four experiments were performed on 340 male CFI mice to determine the effects of morphine and other agents on brain gamma-hydroxybutyrate (GHB) levels. Gas chromatographic analysis demonstrated that morphine produced a significant elevation of GHB levels, the increase occurred primarily in “subcortical” areas, these effects were blocked by pretreatment with naloxone, nonanalgesics failed to produce the same effect, the effect failed to occur in morphine-tolerant animals, the dose-response curve of the effect of morphine on GHB was nonlinear, and brain levels following morphine roughly follow the time course of analgesia.

SHERMAN, A.D. and MITCHELL, C.L. Effects of morphine and pain on brain intermediary metabolism. Neuropharmacology 11: 871-878 (1972)

Three studies were performed to determine (1) whether morphine produced different biochemical effects in the presence and absence of pain and (2) whether these differential effects could be related to analgesia.

In Experiments I and II, 3-day-old chickens were given either saline or morphine and were exposed to pain or not. After testing, animals were frozen in liquid nitrogen and brains analyzed for acids of the Krebs cycle plus pyruvate and lactate by gas chromatography. In Experiment III, the effect of malonic acid (a competitive inhibitor of metabolism of several acids) on analgesia was determined in chickens.

The results of Experiments I and II agreed closely, and an interaction between drug (morphine vs saline) and test (pain vs no pain) was shown by analysis of variance. Morphine without pain depressed whole-brain levels of many acids, as did pain, but the combination of morphine and pain, instead of producing a further decrease, produced an increase in many levels. Prevention of this increase by malonate significantly reduced the effectiveness of morphine.

The data suggests that, in evaluation of morphine, the behavioral state of the organism must be considered since it may change the metabolic state on which the drug acts.

SHERMAN, A. and MITCHELL, C.L. Influence of naloxone and tolerance on citric acid cycle response to morphine and pain. Neuropharmacology 12: 363-366 (1973)

Sherman and Mitchell (1972) have described a drug-test interaction between morphine and pain which consisted of three phases: (1) a reduction in levels of Krebs cycle intermediaries by morphine, (2) a reduction due to pain, and (3) a return toward control levels with the combination of morphine and pain.

Three studies were performed to determine (1) whether the drug-test interaction was also observed in mouse brain or liver, (2) the effect of tolerance on the development of this phenomenon, and (3) the effect of naloxone on this phenomenon.

Male CFI mice were given either saline or morphine and either exposed to analgesic testing or not, then frozen in liquid nitrogen. Brains and livers were analysed for acids of the citric acid cycle by gas chromatography. In experiment II, a tolerant population was used. In experiment III, the effect of naloxone was observed.

In experiment I, the three-part interaction was observed in brain, but not in liver. Experiment II showed that tolerance prevented the occurrence. Experiment III showed that naloxone counteracted the effect of morphine on pain. However, naloxone itself also blocked the alteration in Krebs cycle intermediaries produced by pain. This latter finding argues against these changes in Krebs cycle intermediaries being related to either pain or analgesia but they may be related to some other action of morphine.

SHIH, T., KHACHATURIAN, Z. and BARRY, H. Evidence for cholinergically mediated effect of methylphenidate hydrochloride in the central nervous system. The Pharmacologist 16(2): 242 (1974)

Intravenous injection of methylphenidate HCL (MPH) significantly attenuates single unit activity (UA) in the collateral sensory pathways of the mesencephalic reticular formation in immobilized rats. In further studies, this effect of MPH was mimicked by the cholinergic stimulants nicotine (0.125 and 0.25 mg/kg i.v.) and oxotremorine (OXO: 0.5 and 1 mg/kg i.v.). The effect of MPH was abolished by the nicotinic blocker mecamylamine HCL, 4 mgs/kg i.v., but was not affected by the muscarinic blocker atropine sulfate, 4 mgs/kg i.v. The attenuation UA was only slightly reduced when catecholamines and serotonin were depleted by pretreatment with reserpine (5 mgs/kg i.p.) at 3 hours before MPH or OXO. These results suggest that inhibitory effects of MPH in the collateral sensory pathways of the MRF might be mediated by the cholinergic system.

SHISH, T.M. and OSKOUI, M. The effects of delta-1-tetrahydrocannabinol (delta-1-THC or delta-9-THC) and ethanol on monosynaptic and polysynaptic transmission in the central nervous system. Federation Proceedings 32: 756 (1973)

The effects of delta-1-THC on monosynaptic (MS) and polysynaptic (PS) potentials (P), post-tetanic potentiation (PTP), heart rate (HR), and blood pressure (BP) were studied in anesthetized spinal cats. Administration of delta-1-THC (2.5 and 5.0 mg/kg i.v.) effectively resulted in bradycardia, hypotension and depression of MSP in all experiments. No marked change occurred in the areas under the PSP; however, some changes did occur in their configuration. MSP was depressed maximally by 30-73% of the control, occurring 30 to 105 minutes after a high dose of delta-1-THC (5.0 mg/kg) and recovering completely after $3\frac{1}{2}$ to $4\frac{1}{2}$ hours. The dose of 2.5 mg/kg produced a similar but lesser response. No direct relationship between the change in blood pressure and the observed changes in MS responses could be established. The percentage increased in MSP following tetanus was greater after delta-1-THC; however, the absolute PTP value was less than the control PTP. Ethanol, the solvent, has very little effect on all measured parameters. It is concluded that delta-1-THC depresses spinal MS activity, and that this alteration occurs independently of changes in blood pressure.

SHUSTER, L. Some biochemical effects of morphine on cultured brain cells. Intra-Science Chemical Reports 8: 149-160 (1974)

SHUSTER, L. Tolerance and physical dependence. Biochemical Pharmacology of Narcotic Drugs. Edited by D.H. Clouet. New York: Plenum Press, 1971.

SIMON, E.J. The effects of narcotics on cells in tissue culture. Axenic Mammalian Cell Reactions. Edited by G. Tritsch. New York: Marcel Dekker, Inc., 1969.

SIMON, E.J. Effects of narcotics on the giant axon of the squid. Journal of Neurochemistry. 17: 881-887 (1970)

Levorphanol (10^{-3} M) reversibly blocked conduction in the giant axon of the squid and axons from the walking legs of spider crab and lobster. Similar concentrations of levallorphan and dextrorphan blocked conduction in the squid giant axon. Under the same experimental condition morphine caused an approximately 40 per cent decrease in spike height. Levorphanol did not affect the resting potential or resistance of the squid axon. Spermidine, spermine and dinitrophenol had little or no direct effect on the action potential nor did they alter the potency of levorphanol. Concentrations of levorphanol as low as 5 x 10^{-5} M blocked repetitive or spontaneous activity in the squid axon induced by decreasing the divalent cations in the medium. After exposure to tritiated levorphanol, the axoplasm and envelope of the squid axon accumulated up to 500 per cent of the concentration of tritium found in the external medium, dependent on time of exposure, and other variables. At pH 6 the levels of penetration were 33-50% of those found at pH 8, which correlates with our observation that levorphanol is about 33% as potent in blocking the action potential at pH 6. The penetrability of levorphanol was not affected by spermidine, dinitrophenol or cottonmouth moccasin venom. Levorphanol did not alter the penetration of /C^{14}/acetylcholine nor did it render the squid axon sensitive to it. The block of axonal conduction by compounds of the morphine series is discussed both as to possible mechanisms and significance.

SIMON, E.J. In search of the opiate receptor. American Journal of the Medical Sciences 226(3): 160-168 (1973)

SIMON, E.J. Lipids (and drugs of dependence). Chemical and Biological Aspects of Drug Dependence. Edited by S.J. Mule and H. Brill. Cleveland, Ohio: Chemical Rubber Company Press, 1972.

SIMON, E.J. Morphine and related drugs. Methods in Enzymology, Vol. 34, Part B. Edited by W. B. Jacoby. New York: Academic Press. 1974.

SIMON, E.J. Opiate receptors in animal and human brain. Proceedings of the 9th Congress of Neuropsychopharmacology, Paris, France, 1974.

SIMON, E.J. Sites of action of narcotic analgesic drugs in single cells. Narcotic Drugs: Biochemical Pharmacology. Edited by D.H. Clouet. New York: Plenum Press, 1971. Pp. 310-341.

SIMON, E.J., GARWES. D.J. and RAND, J. Reversible inhibition of RNA phage replication and macromolecular synthesis by levorphanol. Biochemical and Biophysical Research Communications 40(5): 1134 (1970)

Reproduction of RNA phages MS2 and Q_{beta} and the synthesis of phage RNA and protein are markedly inhibited (greater than 99%) by levorphanol. Even at concentrations which are virtually without effect on the host, phage yield is decreased 85%-90%. Levorphanol is most effective when added before or at the time of infection, but no inhibition is observed when it is added 30 minutes or more after infection. Inhibition of phage reproduction is reversed when, even after exposure to levorphanol for an hour, the infected cells are washed free of drug. An effect of levorphanol on an early event in phage replication is postulated.

SIMON, E.J., HILLER, J.M., GROTH, J. and EDELMAN, I. Further properties of stereospecific opiate binding sites in rat brain: On the nature of the sodium effect. The Journal of Pharmacology and Experimental Therapeutics (in press)

SIMON, E.J., SCHAPIRA, L. and WURSTER, N. Effect of levorphanol on putrescine transport in Escherichia coli. Molecular Pharmacology 6(6): 577 (November, 1970)

The disappearance of cellular putrescine observed when Escherichia coli cultures were treated with levorphanol was shown to be largely the result of an acceleration of putrescine efflux produced by the drug. The efflux of putrescine from E. coli exhibited a stringent requirement for metabolic energy. It was found to be greatly reduced by carbon source starvation, by treatment with metabolic inhibitors, or by low temperature. The efflux of putrescine stimulated by levorphanol was also virtually abolished by such treatments. Levorphanol also inhibited the uptake of putrescine by E. coli cells. Evidence is presented which indicates that the inhibition of uptake and the stimulation of efflux represent separate effects of levorphanol. Competition between levorphanol and putrescine for a carrier or binding site was ruled out by kinetic experiments, which showed that inhibition of putrescine uptake by levorphanol was not competitive. The effect of levorphanol on the putrescine pool was readily reversible. Replenishment began without measurable delay upon removal of the drug. Levorphanol also produced reversible alterations in the permeability of E. coli to most, if not all, amino acids, spermidine, and K^+. Possible mechanisms of the effects of levorphanol on cell membranes are discussed.

SJOQVIST, F. and LASAGNA, L. The hypnotic efficacy of doxylamine. Clinical Pharmacology and Therapeutics 8(1): 48-54 (1967)

The efficacy of doxylamine succinate as a nighttime hypnotic was compared with that of placebo and a standard drug, secobarbital sodijm, using a double-blind, randomized black design and replicate observations. The study was performed in 22 hospitalized patients with chronic disease who were accustomed to taking nightly hypnotics. Doxylamine, in doses of 25 and 50 mg., was found to be an effective hypnotic drug, with little difference in the performance of the two doses. Doxylamine performed generally better than secobarbital, 100 mg., but was somewhat inferior to secobarbital, 200 mg. Although the active treatments were significantly better than placebo, 50 per cent of the patients reported satisfactory sleep on dummy medication. Side effects were mild with little difference between the different drugs and placebo except for "hangover," which occurred more often after doxylamine and secobarbital.

SLOTKIN, T.A. and ANDERSON, T.R. Chronic morphine administration alters epinephrine uptake in rat adrenal storage vesicles. Neuropharmacology (in press)

Chronic administration of morphine in rats altered the kinetics of epinephrine uptake into adrenal medullary storage vesicles measured in vitro. In controls, the Michaelis constant for epinephrine was 50.5 ± 2.9 mu-M and maximal uptake was 16. 5 ± 0. 9 nmol/100 mu-g of endogenous catecholamines: after chronic morphine, the Michaelis constant was 92.2 ± 7.5 mu-M and maximal uptake was 21.1 ± 1.6 nmol/100 mu-g of endogenous catecholamines. These data suggest that morphine alters the storage vesicle membrane transport system as well as affecting intravesicular binding of amines.

SLOTKIN, T.A. and ANDERSON, T.R. Sympatho-adrenal development in preinatally-addicted rats. International Journal of Addictive Diseases (in press)

Chronic morphine administration in adult rats results in neurogenic secretion of adrenal catecholamines and compensatory increases in basal catecholamine levels, in activities of catecholamine biosynthetic enzymes and in the number of storage vesicles in the tissue. Perinatally addicted developing rats demonstrated changes completely different from those seen in adults; catecholamine levels and dopamine beta-hydroxylase activity were reduced compared to controls and no induction of tyrosine hydroxylase was observed. The time course of adrenomedullary maturation was delayed through the first 10-20 days of age, with reduced numbers of storage vesicles and larger proportions of partially filled vesicles. On exposure to morphine, continued until weaning, perinatally addicted rats did not display any of the changes in catecholamine synthesis or uptake seen in adult rats. The differences between adults and developing rats can be partly explained by the absence of functional innervation of the neonatal adrenal medulla.

SLOTKIN, T.A., ANDERSON, T.R., SEIDLER, F.J. and LAU, C. Inhibition of epinephrine and metaraminol uptake into adrenal medullary vesicles by aralkyl and alkylamines. Biochemical Pharmacology (in press)

Two amine uptake mechanisms appeared to 'operate in isolated adrenal medullary storage vesicles; one site had a high affinity for epinephrine (K_m ~ 30 mu-M) and low capacity (U_{max} ~ 20 nmols/100 mu-g of endogenous catecholamines), while the other had a low affinity (K_m ~ 2 mM) and a higher capacity (U_{max} ~ 130 nmols). The low affinity site was non-specific and did not display competitive inhibition by agents which affected the high affinity, stimulated transport system. The high affinity system was inhibited in a purely competitive fashion by a variety of indoleamines and phenethylamines, but the two classes of compounds displayed different structure-activity relationships. Substitution on the alpha-carbon decreased the abilities of indoleamines to inhibit stimulated epinephrine uptake, but enhanced activity of phenethylamines. Ring hydroxylation reduced, and methoxylation eliminated, the inhibitory activity of tryptamine, but the same substituents markedly enhanced the activity of phenethylamines. Studies of compounds with restricted side-chain conformation indicated that a condensed structure favored activity in indoleamines while an extended chain enhanced inhibition by phenethylamines.

SMITH, A.A. Adrenergic regulation of the lenticular response to opioids in mice. The Addictive States, Vol. 46. Baltimore, Maryland: The Williams and Wilkins Company, 1968.

The transient lenticular opacities produced in mice by parenteral injections of opioids are of central nervous system origin. Neither cervical ganglionectomy nor adrenalectomy blocks the lenticular action of levorphanol.

Tolerance develops quickly to the lenticular action of a single dose of this opioid. Short term tolerance to a second levorphanol dose may appear within 30 minutes of the first levorphanol dose and may last up to 8 hours. Long term tolerance develops more gradually and may persist 3 weeks. The two phenomena seem to be independent of each other.

Long term tolerance is blocked by the prior administration of actinomycin or puromycin. These antibiotics do not affect development of short term tolerance. Development of long term tolerance is also blocked by anesthetic doses of chloroform or ethanol.

Smith, A.A. continued

It was shown that lenticular tolerance develops in mice treated with reserpine and, for that reason, it was concluded that the sites of opioid and adrenergic actions are different. Because levallorphan prevented the development of tolerance to levorphanol, the sites for initiating lenticular opacities and for producing tolerance are thought to be similar. In the tolerant mouse, catecholamines fail to potentiate fully the lenticular activity of levorphanol. It is suggested, therefore, that tolerance may not develop to the opioid directly but in relation to the adrenergic portion of the response.

SMITH, A.A. Anamnestic response to an opioid. Experientia 27: 542 (1971)

SMITH, A. Narcotic antagonists. Narcotic Drugs: Biochemical Pharmacology. Edited by D.H. Clouet. New York: Plenum Press, 1971.

SMITH, A.A. Potentiation of opioid-induced cataracts by catecholamines injected into the mouse brain. Psychopharmacologia 16: 313-317 (1970)

The cataractogenic effect of parenteral levorphanol was increased by the injection of catecholamines into the mouse brain. Although L-epinephrine potentiated this effect most strongly, the potency of DL-isoproterenol unexpectedly equaled that of L-norepinephrine. Phenoxybenzamine, however, blocked the effect of L-norepinephrine, whereas pronethalol failed to inhibit DL-isoproterenol. That DL-isoproterenol may act indirectly is supported by the finding that treatment of the mouse with reserpine blocked the potentiation induced by DL-isoproterenol but did not inhibit the action of the pressor catecholamines.

SMITH, A.A. and HUI, F.W. Inhibition of neurotrophic activity in salamanders treated with opioids. Experimental Neurology 39(1): 36 (1973)

Regeneration of the amputated hind limb of the salamander was prevented by the injection of methadone or levorphanol. Blastema failed to develop despite formation of a thick epidermal cap at the wound site. Injection of the narcotic antagonist, levallorphan, blocked blastemal development for 4 wk but normal growth then began. Phalanges appeared 4 wk later than in controls. Naloxone, a potent narcotic antagonist without agonist activity, neither altered blastemal development nor prevented normal regeneration and differentiation. Treatment with the opioids methadone or levorphanol produced some atrophy of the lingual epithelium and taste buds of the salamanders. Neither of the antagonists caused these changes.

SMITH, A.A., HUI, F. and CROFFORD, M. Inhibition of growth by methadone and other cholinolytic drugs. Annals of the New York Academy of Sciences 228: 338-343 (March, 1974)

Hemicholinium-3 or triethylcholine administered daily to salamanders blocked regeneration of their amputated hind limb and caused atrophy of their taste buds. These drugs act primarily by blocking synthesis of acetylcholine (ACh). Injection of the salamander with methadone (2 mg/kg) or with levorphanol (10 mg/kg) also prevented regeneration of the amputated hind limb. Blastema failed to develop despite formation of a thick epidermal cap at the wound site. The antagonist, levallorphan (10 mg/kg), which also possesses agonistic activity, initially blocked blastemal development for four weeks, but then normal growth began. Phalanges

Smith, A. A., Hui, F. and Crofford, M. continued
appeared four weeks later than control. Naloxone, the pure antagonist, neither altered blastemal development nor prevented normal regeneration and differentiation. Treatment with the opioids methadone or levorphanol produced some atrophy of the lingual epithelium and of the taste buds of the salamander. Atrophy of taste buds suggests a peripheral action for opioids. Newborn mice treated daily with methadone (2 mg/kg-4 mg/kg) for up to six weeks grew far more slowly than did saline-treated littermates. Concomitant naloxone treatment prevented growth inhibition. The adverse effects of cholinolytic drugs on growth of salamanders suggests that the action of methadone in retarding growth of mice may be related to the ability of this opioid to inhibit the release of acetylcholine. Preliminary results suggests that growth retardation induced by methadone is targeted in part for nervous tissue, as suggested by the reduced uptake of injected radioactive leucine by the brain, as compare to the liver.

SMITH, A. A., KARMIN, M. and GAVITT, J. Tolerance to the lenticular effects of opiates. The Journal of Pharmacology and Experimental Therapeutics 156(1): 85 (1967)

Opiates, when injected in large doses, induce transient lenticular opacities in mice. In this study it was found that a single previous dose of levorphanol established long-term resistance or tolerance to the lenticular effects of a second dose. However, high concentrations of epinephrine instilled in the eyes of tolerant mice were able to restore the normal lenticular response to parenteral levorphanol. The epinephrine concentrations required for an ED50 response correlated with the size of the first dose of levorphanol. Morphine or methadone, when substituted for the first dose of levorphanol, produced a cross-tolerance to the second dose of levorphanol as measured in terms of an epinephrine concentration. When larger doses of levorphanol were given, short-term tolerance also was observed. This effect developed within 30 min and persisted For up to 8 hr. Lenticular tolerance was found to develop in mice previously treated with reserpine, suggesting that this phenomenon probably does not require adrenergic mediation. Levallorphan was able to prevent the development of long-term tolerance when given in a large dose relative to the dose of levorphanol. The antibiotics actinomycin or puromyciri also blocked long-term tolerance development, although neither of these inhibitors of protein synthesis prevented the appearance of short-term tolerance. Evidently, long-term lenticular tolerance to opiates is a complex phenomenon involving a decreased sensitivity to instilled epinephrine that may be related to the formation of an inhibitory protein.

SMITH, C.B. Neurotransmitters and the narcotic analgesics. Chemical and Biological Aspects of Drug Dependence. Edited by S.J. Mule and H. Brill. Cleveland, Ohio: Chemical Rubber Company Press, 1972. Pp. 495-504.

Among the drugs which produce dependence, the narcotic analgesics have specific effects upon the content and turnover of various neurotransmitters in the brain. Acute administration of these drugs prevents the release of acetylcholine and causes an accumulation of this substance in the brains of various species. Tolerance to these effects develops when the narcotic analgesics are administered over prolonged periods of time. These effects of the narcotic analgesics are specifically blocked by narcotic antagonists. Acute administration of the narcotic analgesics also causes decreases in brain catecholamine content and increases the synthesis and turnover of both dopamine and norepinephrine in the brain. Tolerance develops to morphine-induced changes in brain catecholamine turnover when

Smith, C.B. Neurotransmitters. . . continued
narcotic analgesics are administered chronically. Specific narcotic antagonists block the effects of the narcotic analgesics upon catecholamine turnover in the brain. The acute administration of the narcotic analgesics does not have pronounced effects upon brain serotonin content. Changes in the rates of turnover of acetylcholine, dopamine, norepinephrine, and serotonin have been related to the dependent state produced by chronic administration of the narcotic analgesics.

SMITH, C.B. and SHELDON, M.I. Effects of narcotic analgesic drugs on brain noradrenergic mechanisms. Agonist and Antagonist Actions of Narcotic Analgesic Drugs. Edited by H.W. Kosterlitz, H.O. Collier and J.E. Villarreal. Baltimore, Maryland: Baltimore University Park Press, 1973.

SMITH, C.B., SHELDON, M.I., BEDNARCZYK, J.H. and VILLARREAL, J.E. Morphine-induced increases in the incorporation of ^{14}C-tyrosine into ^{14}C-dopamine and ^{14}C-norepinephrine in the mouse brain: Antagonism by noloxone and tolerance. The Journal of Pharmacology and Experimental Therapeutics 180(3): 547-557 (1972)

For abstract, see Section II. Drug Chemistry and Metabolism.

SNYDER, S.H. Putative neurotransmitters in the brain: Selective neuronal uptake, subcellular localization, and interactions with centrally acting drugs. Biological Psychiatry 2: 357-389 (1970)

For abstract, see Section II. Drug Chemistry and Metabolism.

SNYDER, S.H., TAYLOR, K.M., COYLE, J.T. and MEYERHOFF, J.L. The role of brain dopamine in behavioral regulation and the actions of psychotropic drugs. American Journal of Psychiatry 127(2): 199-207 (August, 1970)

By comparing biochemical and behavioral actions of d- and l- isomers of amphetamine, the authors show that locomotor hyperactivity, an animal model for the central stimulant effects of amphetamine, is mediated by brain norepinephrine. By contrast, stereotyped, compulsive gnawing behavior in rats, which resembles symptoms of amphetamine psychosis, appears to be regulated by brain dopamine. Since haloperidol, a potent blocker of dopamine receptors, is uniquely efficacious in treating Gilles de la Tourette's disease, the authors suggest that hyperactivity of dopamine systems in the brain may be a factor, in the pathophysiology of this condition.

SOFIA, R.D., DIXIT, B.N. and BARRY, H., III. The effect of delta-l-tetrahydrocannabinol in serotonin metabolism in the rat brain. Life Sciences 10(1): 425-436 (1971)

Cerebellum were most affected and apparently accounted for the overall increase seen in the whole brain levels of 5-HT. Since delta-1-THC did not affect MAO activity, the increase in 5-HT was evidently not due to inhibition of its degradation. However, synthesis rate of 5-HT was significantly reduced (50 percent) by delta-1-THC. Furthermore, pretreatment with delta-l-THC retarded the rate of reserpine-induced depletion of brain 5-HT. Alteration of the vesicular membrane is suggested as a possible mechanism for the effects of delta-1-THC on 5-HT metabolism.

SOFIA, R.D., ERTEL, R.J., DIXIT, B.N. and BARRY, H. The effect of delta-l-tetrahydrocannabinol on the uptake of serotonin by rat brain homogenates. European Journal of Pharmacology 16: 257-259 (1971)

The uptake of (14)C-serotonin by rat brain homogenates (synaptosomes) was inhibited by delta-1-tetrahydrocannabinol in concentrations of 1 x 10(-7)M and greater. The antidepressant agent desipramine had the same effect but showed greater potency, with a concentration as low as 1 x 10(-8)M being needed to inhibit (14)C-serotonin uptake.

SOKOL, G.H. and MAICKEL, R.P. Toxic interactions of d-amphetamine and tricyclic antidepressants in mice. Research Communications in Chemical Pathology and Pharmacology 3(3): 513 (May, 1972)

The interaction of various tricyclic drugs with d-amphetamine toxicity has been studied under standard conditions in non-aggregated mice. Pre- or post-treatment with promazine protects the animals in all cases. The tertiary amines, imipramine and amitriptyline, have either no effect or exert a protective action, while the secondary amines, desmethylimipramine and nortriptyline, either potentiate or reduce the toxicity of d-amphetamine, depending on the dosage schedule with respect to time.

SORENSEN, J.P., JR. and HARVEY, J.A. Decreased brain acetylcholine after septal lesions in rats: Correlation with thirst. Physiology and Behavior 6: 723-725 (1971)

Bilateral lesions in the septal area of the forebrain produced both a significant decrease in brain content of acetylcholine and a significant increase in daily water consumption. Only lesioned rats showing hyperdipsia demonstrated a decrease in brain acetylcholine. These data support previous suggestions that thirst is mediated by a cholinergic mechanism in brain.

SPARBER, S.B. Neorochemical changes associated with schedule-controlled behavior. Federation Proceedings (in press)

SPAULDING. T.C., FORD, R.D., DEWEY, W.L., McMILLAN, D.E. and HARRIS, L.S. Some pharmacological effects of phenitrone and its interaction with delta-9-THC. European Journal of Pharmacology 19: 310-317 (1972)

For abstract, see Section II. Drug Chemistry and Metabolism.

SPAULDING, T.C., MINIUM, L., KOTAKE, A.N. and TAKEMORI, A.E. The effect of diazepam on the metabolism of methadone by the liver of methadone-dependent rats. Drug Metabolism and Disposition 2(5): 458-463 (1974)

For abstract, see Section II. Drug Chemistry and Metabolism.

STEELE, W.J. and JOHANNESON, T. Effects of morphine infusion in maternal rats at near term on ribosome size distribution in foetal and maternal rat brain. Acta Pharmacologia et Toxicologia (in press)

STEELE, W.J. and JOHANNESON, T. Effects of prenatally administered morphine on brain development and resultant tolerance to the analgesic effect of morphine in offspring of morphine treated rats. Acta Pharmacologia et Toxicologia (in press)

STEINERT, H.R., HOLTZMAN, S.G. and JEWETT, R.E. Some agonistic actions of the morphine antagonist levallorphan on behavior and brain monoamines in the rat. Psychopharmacologia 31: 35-48 (1973)

The effects of levallorphan, a narcotic-antagonist analgesic, were studied on locomotor activity, operant behavior (continuous avoidance schedule), and brain monoamine content in the rat. Levallorphan produced an increase in locomotor activity and in the rate of avoidance responding. Brain norepinephrine was significantly decreased 1 h after 256 mg/kg of levallorphan. Brain dopamine (DA) levels were lowered by 64 and 256 mg/kg of levallorphan. There was no effect on brain serotonin levels. The stimulant effects of levallorphan on operant behavior were blocked by simultaneous administration of naloxone. A clear antagonism of the effects of levallorphan on locomotor activity by naloxone could be demonstrated for low doses of levallorphan but not for doses above 16 mg/kg. Naloxone also failed to prevent the depletion of brain catecholamines produced by levallorphan. Naloxone alone had no consistent effect on either of the behaviors under observation or on brain monoamine content. These findings indicate that levallorphan is a stimulant of behavior in the rat, and that the stimulant action is mediated by at least two mechanisms: one which is blocked by naloxone, and one which is not. Furthermore, it is suggested that the rat should be considered as a possible animal model in which to study the agonistic properties of certain narcotic-antagonist analgesics on behavior.

STERNBACH, D.D., ABOOD, L.G. and HOSS, W. A benzilate ester of pyrrolizidine and its stereochemical relationship to other psychotomimetic glycolates. Life Sciences 14: 1847-1856 (19'74)

For abstract, see Section I. Methodology of Drug Research.

STOELTING, R.K., MARTZ, R.C., GARTNER, J., CREASSER, C., BROWN, D.J. and FARNEY, R.B. Effects of delta-9-tetrahydrocannabinol on halothane MAC in dogs. Anesthesiology 38(61: 521-524 (June, 1973)

For abstract, see Section II. Drug Chemistry and Metabolism.

STOLMAN, S. and ASTON, R. Relationship of barbital disposition to auto-induced hypersusceptibility in the rat. Biochemical Pharmacology 19: 595-601 (1970)

Two daily doses of barbital induce, in the female rat, a hypersusceptibility to the drug which is present after 18 days, and absent after 38 days of abstinence. Spectrophotometric and radiometric assays of barbital tissue levels, at various times from 10 to 360 min after drug administration, reveal no differences in blood, brain or urinary barbiturate levels among control, hypersusceptible or posthypersusceptible animals. The data support the suggestion that induced hypersusceptibility does not result from changes in the disposition of barbiturate in vivo. It appears likely that this phenomenon results from central nervous system alterations in the localization of, or sensitivity to, the drug.

STOLMAN, S. and ASTON, R. The role of anoxia and hypercarbia in induced hypersusceptibility to barbital. Archives internationales de Pharmacodynamie et de Therapie 180(1): 40 (July, 1969)

The phenomenon of hypersusceptibility to a barbiturate, occurring several weeks following two daily doses of the drug, has been previously reported from this laboratory. This response has been shown to be unrelated to alterations in the in vivo disposition of barbiturates. Such auto-induced hypersusceptibility might, however, be due to non-specific central nervous system damage resulting from cerebral hypoxia or hypercarbia coincident with the effects of the initial administration of barbiturate. The present study was designed to investigate the possibility that hypoxic or hypercarbic brain damage might be responsible for the later manifestation of an exaggerated response to these drugs.

SULSER, F. On the mode of action of antidepressants. Psychopharmacologic Treatment in Psychiatry. New York: Marcel Dekker. Inc., 1973.

TAKEMORI, A.E. Biochemistry of drug dependence. Annual Review of Biochemistry 43: 15-33 (1974)

TAKEMORI, A.E. and TULUNAY, F.C. Further studies on the receptor alteration induced by morphine. The Pharmacologist 15: 242 (1973)

In an earlier study, it was shown that pretreatment of mice with M resulted in a significant increase of the apparent pA_2 of morphine-naloxone which suggested an alteration of the analgesic receptor. The magnitude of this increase indicated a two-fold increase in the apparent affinity constant (K_B) of naloxone (N) for the receptor. Mice were made highly tolerant to the analgesic effect of M by implantation of M pellets for 3 days. The apparent pA_2 increased significantly from 6.9 in control mice to 7.8 in tolerant mice. This indicates that the apparent K_B of N for the receptor was increased by over 7 fold and that a qualitative rather than a quantitative change took place on the receptor. Cycloheximide (CHX. 25mg/kg) 12 hr before M pretreatment did not alter the ED50 of M or the increased efficacy of N. However, daily injections of CHX (20 mg/kg) for 7 days (4 days prior to M implantation and 3 days during the implant) inhibited the development of tolerance by 84% and the increased efficacy of N by 64%. The increased affinity of N due to M treatment appears related to the development of tolerance, The possibility that N may act at an allosteric site to produce an apparent competitive antagonism is suggested.

TAYLOR, K.M. and SNYDER, S.H. Amphetamine: Differentiation by d and 1 isomers of behavior involving brain norepinephrine or dopamine. Science 168: 1487-1489 (June 19, 1970)

d-Amphetamine is markedly more potent an inhibitor of catecholamine uptake by norepinephrine neurons in the brain than is l-amphetamine, whereas the two isomers are equally active in inhibiting catecholamine uptake by the dopamine neurons of the corpus striatum. In behavioral studies, d-amphetamine is ten times as potent as l-amphetamine in enhancing locomotor activity, while it is only twice as potent in eliciting a compulsive gnawing syndrome. This suggests that the locomotor stimulation induced by amphetamine involves central norepinephrine, while dopamine neurons play an important role in the induced compulsive gnawing behavior. Assessment of differential actions of d- and l-amphetamine may be an efficient method to differentiate behaviors involving norepinephrine or dopamine in the brain.

TAYLOR, W.A. and SULSER, F. Effects of amphetamine and its metabolites on cerebral noradrenergic mechanisms. The Journal of Pharmacology and Experimental Therapeutics 185(3): 620-632 (1973)

TAYLOR, W.A. and SULSER, F. Effects of intraventricularly administered l- d- and dl-p-hydroxyamphetamine (POH) on behavior and cerebral catecholamines. Presented at the Fifth International Congress on Pharmacology, San Francisco, California, 1972.

TESCHEMACHER, H., OPHEIM, K. and GOLDSTEIN, A. Nonspecific photochemical attachment of opiates to brain tissue. Proceedings of the Sixth International Congress of Pharmacology, Helsinki, Finland, July 20-25, 1975.

TILSON, H.A., RECH, R.H. and SPARBER, S.B. Release of ^{14}C-norepinephrine into the lateral cerebroventricle of rats exposed to a conditioned aversive stimulus. Pharmacology Biochemistry and Behavior (in press)

Rats chronically implanted with push-pull cannulas were injected with a pulse of [^{14}C] -norepinephrine (NE) injected into the lateral cerebroventricle under a variety of pretreatment and behavioral conditions. Subjects pretreated intraventricularly with 6-hydroxydopamine (Group A) or ascorbic acid vehicle (Group B) were subsequently perfused under four conditions: (I) presentation of a novel, visual stimulus in a one-way avoidance chamber; (II) presentation of the light (CS) followed by shock; (III) training to a high level of avoidance behavior, after which the CS was presented in the absence of opportunity for an avoidance response and in the absence of shock; and (IV) after forced extinction, followed by CS without opportunity to avoid and without presentation of shock. Samples of perfusate were analyzed for total [^{14}C] in a scintillation counter and for proportion of NE and normetanephrine (NM) by TLC from rats subjected to the four test conditions. During tests I and IV the [^{14}C] perfusion "wash-out" did not differ from control values for either Group A or B. During test II, total radioactivity as well as the proportions of NE and NM increased in the perfusate for both Grous A and B. Presenting the CS without shock (III) resulted in an increase in [^{14}C] and NE and NM for Group B (vehicle), but not for Group A (6-OHDA). To test for non-specific release unrelated to a brain catecholaminergic function, another group of rats was subjected to identical treatments with the exception that [^{14}C]-urea replaced [^{14}C]-NE as a pulse-label. In these subjects test II (shock) induced an increase in [^{14}C] in the perfusate, while tests I, III and IV yielded wash-out curves essentially identical to controls.

TINKLENBERG, J.R. Study group (ad hoc): Cannabis study group on marihuana and alcohol. Psychopharmacology Bulletin 8(1): 9-10 (1972)

Moderate doses of marihuana and alcohol used in the study induced significant cognitive changes from placebo conditions and baseline predrug performances only in time production tasks. There were, however, consistent trends suggesting marihuana was somewhat more disruptive of tasks which required appropriate temporal sequencing and that marihuana induced greater variability in cognitive performance. Marihuana consistently increased amplitudes of AEP and CNV in electrocortical measures. Moderate doses of marihuana and alcohol induce minor alterations along simple cognitive dimensions. There are concomitant electrocortical changes which more appreciably differentiate the 2 drugs.

TOLOSA, E.S. and SPARBER, S.B. Apomorphine in Huntington's Chorea: Clinical observations and theoretical considerations. Life Sciences 15: 1371 (1974)

Five patients, four definitively diagnosed as suffering from Huntington's disease and the fifth with abnormal involuntary movements (AIM) and dementia but no apparent family history of the disease, were administered apomorphine. Although the short duration of action and stressful side-effects produced by apomorphine limited its use regarding a complete dose- and time-response evaluation, slight to marked diminution of AIM was seen in all patients. Optimal doses ranged from 1-2 mg across patients, producing a significant reduction in AIM for the entire hour of observations. Theoretical interpretations of these effects regarding dopaminergic receptor stimulation and/or blockade by apomorphine are discussed.

TRUITT, E.B., JR. and ANDERSON, S.M. Biogenic amine alterations produced in the brain by tetrahydrocannabinols and their metabolites. Annals of the New York Academy of Sciences 191: 68-73 (1971)

For abstract, see Section II. Drug Chemistry and Metabolism.

TRUITT, E.B., JR. and ANDERSON, S.M. The role of biogenic amines in the central actions of tetrahydrocannabinols and their metabolites. Acta Pharmaceutica Suecica 8: 696-697 (1971)

For abstract, see Section II. Drug Chemistry and Metabolism.

TSENG, L.F., WEI, E. and LOH, H.H. Brain areas associated with bulbacapnine catalepsy. European Journal of Pharmacology 22: 363-366 (1973)

Bulbocapnine is the prototype of chemical agents used in the experimental study of catalepsy (DeJong, 1945). Based on the structural similarity of bulbocapnine to apomorphine, a postulated dopaminergic receptor agonist (Ernst and Smelik, 1966; Roos, 1969; Anden et al., 1967). Ernst (1969) suggested that bulbocapnine may act by blocking dopaminergic receptors in the striatum. Administered systemically, bulbocapnine will antagonize d-amphetamine-stimulated stereotyped behavior (Tseng and Walaszek, 1972). Apomorphine, in turn, will antagonize bulbocapnine-induced catalepsy (Divry and Evrard, 1934). Stille and Lauener (1971) observed a correlation between the cataleptic effect of bulbocapnine and the increase of striatal homovanillic acid. These studies indicate a reciprocal interaction between bulbocapnine and brain dopaminergic mechanisms. In this investigation, we attempted to localize, by intracerebral micro-injections of bulbocapnine into the rat brain, the neuroanatomical sites related to bulbocapnine catalepsy. The results indicate that bulbocapnine acts in the striatum to produce catalepsy.

TULUNAY, F.C., SPARBER, S.B. and TAKEMORI, A.E. The role of dopaminergic stimulation and blockade on the nociceptive and antinociceptive responses of mice. European Journal of Pharmacology (in press)

Agents which stimulate dopaminergic receptors directly or indirectly such as apomorphine and L-dopa, increased the reactivity of mice to a nociceptive stimulus. The increased reactivity was pharmacologically quantitated by estimating the hyperalgesic ED50 to be 4.4 and 115 mg/kg for apomorphine and L-dopa, respectively. This hyperalgesia was blocked by the dopamine receptor blocking agents, haloperidol and pimozide, but not by the narcotic antagonist, naloxone. Apomorphine antagonizes morphine analgesia however the induced hyperalgesia only accounts for part of the antagonistic activity of apomorphine. The majority of the antagonistic activity of apomorphine appears to be by means other than action on dopaminergic receptors.

TULUNAY, F.C. and TAKEMORI, A.E. Dopaminergic system and analgesia. The Pharmacologist 16: 248 (1974)

We showed earlier that pretreatment of mice with narcotic agonists caused a marked increase in the antagonistic effect of narcotic antagonists and suggested that the increased efficacy of antagonists might be a sensitive indicator of the initiation of tolerance. In the present study we investigated the effect of the dopaminergic system on morphine (M) analgesia and the naloxone (NLX) efficacy using the tail-flick assay in mice. Dopaminergic receptor agonist apomorphine (APO) and L-DOPA produced hyperalgesia (hyperalgesic ED50's were 4.4 (3.1-6.1) and 115.0 (72.8-181.7) mg/kg respectively), and this hyperalgesia was inhibited by dopaminergic receptor blocking agents, haloperidol (HAL) and pimozide (PMZ) but not by NLX. Both APO and L-DOPA caused an increase in M ED50 while HAL decreased it and PMZ was without effect. However NLX shifted the M ED50 in all treated animals proportionately similar to that seen in control mice. In animals pretreated with a single dose of M; L-DOPA, APO and PMZ increased and HAL, decreased the M ED50. The increased efficacy of NLX seen after M pretreatment was again proportionately the same in all treated groups. Our results suggest that the dopaminergic system may play a modulating role in the action of M but not in the efficacy of NLX.

TULUNAY, F.C. and TAKEMORI, A.E. The effect of morphine on the incorporation of ^{3}H-leucine into retinal proteins and subsequent axonal transport in the optic system of rats. Life Sciences (in press)

TULUNAY, F.C. and TAKEMORI, A.E. Further studies on the alteration of analgesic receptor-antagonist interaction induced by morphine. The Journal of Pharmacology and Experimental Therapeutics 190(3): 401-407 (1974)

For abstract, see Section I. Methodology of Drug Research.

TULUNAY, F.C. and TAKEMORI, A.E. The increased efficacy of narcotic antagonists induced by various narcotic analgesics. The Journal of Pharmacology and Experimental Therapeutics 190(3): 395-400 (1974)

For abstract, see Section I. Methodology of Drug Research.

TURKANIS, S.A., CELY, W., OLSEN, D.M. and KARLER, R. The anticonvulsant properties of cannabidiol. Research Communications in Chemical Pathology and and Pharmacology 8(2): 231 (June, 1974)

A series of laboratory tests were conducted in mice to evaluate the anticonvulsant properties of cannabidiol (CBD). The drug abolished hindlimb extension induced by maximal electroshock (MES) and raises the MES (extensor) and 6-Hz-electroshock thresholds, but does not affect the 60-Hz-electroshock or minimal seizures caused by pentylenetetrazol (PTZ). As an anticonvulsant, CBD appears to be more closely related to diphenylhydantoin (DPH) than to its chemical congener, delta-9-tetrahydrocannabinol (delta-9-THC).

UNGAR, G. and GALVAN, L. Conditions of transfer of morphine tolerance to brain extracts. Proceedings of the Society for Experimental Biology and Medicine 130: 287-291 (1968)

VACHON, L., FITZGERALD, M.X., SOLLIDAY, N.H. GOULD, I.A. and GAENSLER, E.A. Single-dose effect of marihuana smoke. New England Journal of Medicine 288: 985-989 (1973)

Normal volunteers with previous marihuana smoking experience inhaled the total smoke from 3.23 mg per kilogram of marihuana, using a bag-in-box technic. Randomly, nine received marihuana containing a high (2.6 per cent), and eight a low (1.0 per cent) concentration of delta-9-tetrahydrocannabinol.

Physiologic variables were monitored before and for 20 minutes after smoking. In the high-dose group the heart rate increased 28 per cent. Concomitantly, airway resistance, measured in a body plethysmograph, fell 38 per cent; the functional residual capacity remained unchanged (± 50 ml) throughout, and specific airway conductance increased 44 per cent. Flow volume loops showed no increase in heart rate but significant, if lesser changes, in airways dynamics. Carbon dioxide sensitivity, measured by rebreathing remained unchanged in both groups.

Marihuana smoke, unlike cigarette smoke, causes bronchodilation rather than bronchoconstriction and, unlike opiates, does not cause central respiratory depression.

VA CHON, L., MIKUS, P., MORRISEY, W., FITZGERALD, M. and GAENSLER, E. Proceedings from the National Conference on Marihuana (in press)

The effects of a single administration of marihuana smoke on bronchial mechanics were studied in a group of asthmatic subjects. The diagnosis of asthma was made on the basis of history and evidence of reversible airway obstruction; the subjects were free of symptoms at the time of testing. They received a standard volume of a mixture of air and smoke from natural marihuana containing one of two different concentrations (1.9% and 0.9%) of delta-9-THC. Both concentrations showed significant and prolonged reversal of the bronchoconstriction as well as significant but shorter duration tachycardia.

VAN VUNAKIS, H., WASSERMAN, E. and LEVINE, L. Specificities of antibodies to morphine. The Journal of Pharmacology and Experimental Therapeutics 180(2): 514-521 (1972)

3-Carboxymethylmorphine was coupled to polylysine with the use of carbodiimide. The conjugates, complexed to succinylated hemocyanin, were used to immunize rabbits and guinea pigs.. Antibody activity, found in the 7 S gamma-globulin fraction of the rabbit serum, increased during the course of immunization. Codeine was most effectively bound to anticarboxymethylmorphine. In order of decreasing effectiveness, dihydrocodeine. morphine, heroin, hydromorphone and nalorphine also cross-react with anti-carboxymethylmorphine. A radioimmunoassay for measurement of these compounds at the picomole level has been developed. Twenty-two of 35 extracts of autopsy sera from cases of sudden death suspected of drug abuse were positive when tested for reaction with the morphine antiserum by this radioimmunoassay.

VESTERGAARD, P., RUBIN, V., BEAUBRUNN, M.H., CRUICKSHANK, E. and PICOU, D. Steroid excretion in chronic cannabis users and matched controls. Acta Pharmaceutica Suecica 8: 671-706 (1971)

A collaborative study is currently under way on Jamaica of the effect of long term use of cannabis. This study has been organized jointly by the Research Institute for the Study of Man in New York (Drs. Rubin and Comitas) and the University of the West Indies (Drs. Beaubrunn and Cruickshank).

AS a subproject of this investigation we have compared steroid excretion patterns in groups of chronic users and matched controls. Apart from creatinine analyses done with Autoanalyzer techniques the methods used have all been developed at the Research Center, Rockland State Hospital. A total of 15 urinary steroids have been determined and two group assays for steroids have been performed on 24 h urines collected on a metabolic ward from a total of 20 subjects from both groups.

There were no significant differences between the two groups in any steroid measurement indicating that prolonged exposure to cannabis in this group of chronic users did not affect adrenal function as evaluated through steroid excretion data.

A collateral study of thyroid function done by another group at the Research Center showed no significant changes in 3 thyroid indices on comparison between non-users and chronic users of cannabis.

VOLICER, L., PURI, S.K. and COCHIN, J. Effect of morphine on phosphodiesterase (PDE) activity in rat striatum. Proceedings of Second International Conference on Cyclic AMP, July 8-11, 1974

Morphine sulfate (MS) affects the dopaminergic system in the striatum. Since dopamine-sensitive adenylate cyclase was found in the striatum, we investigated the effect of MS on the cyclic AMP system. PDE activity in the total homogenate of striatum was measured by the method of Brooker et al. (Biochem, 7, 4177, 1968) using cyclic AMP as a substrate. In vitro MS inhibited PDE activity in a substrate concentration of $3.33x\text{-}10^{-3}$ but not in concentrations of $3.33x10^{-5}$ or $3.33x10^{-7}$ M. This effect was dose dependent in the range of 0.1 to 1000 mu-M concentrations of MS. Administration of MS in vivo (7. 5-30 mg/kg i.p., 1 hr before sacrifice) inhibited the PDE activity only with the high substrate concentration. PDE activity was compared in homogenates from control and MS-treated (15 mg/kg) rats; the kinetic analysis was consistent with a competitive inhibition of PDE activity by MS. Km of cyclic AMP for control rats was $4.4x10^{-4}$M and for MS-treated rats was $6.1x10^{-4}$M. Rats given MS in increasing doses for 14 days developed tolerance to the inhibitory effect of MS on PDE activity. These results indicate that MS selectively inhibits a high K_m PDE in the rat striatum.

VOLLMER, R.R., CAVERO, I., ERTEL, R.J., SOLOMON, T.A. and BUCKLEY, J.P. Role of the central autonomic nervous system in the hypotension and bradycardia induced by (-)-delta-9-trans-tetrahydrocannabinol. Journal of Pharmacy and Pharmacology 26(3): 186-192 (March, 1974)

(-)-Delta-9-trans-tetrahydrocannabinol (delta-9-THC), when given intravenously (2 mg kg^{-1}) to cats, produced marked decreases in blood pressure and heart rate which developed gradually and were of prolonged duration. Cervical spinal transection (C_1-C_2) abolished these effects whereas surgical removal of neurogenic tone to the myocardium selectively eliminated the bradycardia. Bilateral vagotomy alone did not modify the action of delta-9-THC upon heart rate or blood pressure. Recordings of spontaneous sympathetic outflow in the inferior cardiac nerve indicated a rapid reduction in neural discharge rate after delta-9-THC administration. These observations support the hypothesis that delta-9-THC produces a cardiodecellerator and hypotensive effect by acting as some level within the sympathetic nervous system. Experiments conducted to investigate

Vollmer, R.R., Cavero, I., Ertel, R. J., Solomon, T.A. and Buckley, J.P. continued transmission in the superior cervical and stellate ganglia demonstrated that delta-9-THC did not alter ganglionic function. Also, responses to intravenous isoprenaline and noradrenaline were unchanged which suggested that delta-9-THC did not interact with alpha- or beta-adrenoceptors. The possible action of delta-9-THC on central sympathetic structures was investigated by perfusion of delta-9-THC into the lateral cerebral ventricle. Delta-9-THC so administered produced a significant reduction in heart rate without a substantial lowering of blood pressure. Tritiated or ^{14}C-delta-9-THC perfused into the lateral ventricle demonstrated that the amount of radioactive compound passing into the peripheral circulation was insignificant and could not account for the decrease in heart rate. The current data are in agreement with the proposal that delta-9-THC produces cardiovascular alterations by an action on the central nervous system which results in a decrease in sympathetic tone.

VOLAVKA, J., CROWN, P., DORNBUSH, R., FELDSTEIN, S. and FINK, M. EEG, heart rate and mood change ("high") after cannabis. Psychopharmacologia 32: 11-25 (1973)

Fourteen experienced marijuana users smoked marijuana, hashish, delta^9 -THC, and placebo. EEG, ECG and ratings of subjective feelings of "high" and pleasantness were recorded. EEGs were processed. by period analysis.

In EEG, marijuana and delta 9-THC increased the amount of alpha activity, and the three Cannabis preparations decreased the amount of beta activity. The average frequency of alpha activity was decreased by 0.15-0.20 c/sec after marijuana, hashish and delta^9-THC. The. peak EEG effect occurred during the first 10 min after smolcing; most of the changes 'disappeared after 40 min. Heart rate was increased by all the three drugs, and the effect persisted for the entire observation period (50 min).

Feelings of "high" were elicited by each Cannabis preparation. This was not true of the pleasantness of the experience: only marijuana and hashish were perceived as more pleasant than placebo. Intensity of "high" increased with the amount of alpha activity, and decreased with the average alpha frequency. Pleasantness was unrelated to the EEG.

The "high" showed a linear increase with heart rate, whereas pleasantness of the experience was an inverted U-function of heart rate.

VOLAVKA, J., LEVINE, R., FELDSTEIN, S. and FINK, M. Short-term effect of heroin in man. Archives of General Psychiatry 30:677 (May, 1974)

Nineteen detoxified male heroin postaddicts received 25 mg of heroin intravenously, on two occasions, and a placebo intravenously on two other occasions. Two tasks were administered: an auditory detection task to measure performance, and a mood monitoring task to measure the subjective reports of "high." Each task was administered once after heroin and once after the placebo. Electroencephalogram, breathing rate, heart rate, and pupil size were measured before and after each injection. Heroin injections resulted in an increase of heart rate. The time course of these changes and of the heroin "high" was defined.

While an increase in number of omission errors was associated with a decrease in EEG frequency, the rate of increase was differentially affected by heroin and placebo. Admintstration of heroin was followed by a prolongation of reaction time. Intensity of the subjective "high" was negatively related to the EEG frequency, breathing rate, and pupil size. This test battery is useful for measurement of effects of opiates and their antagonists.

VOLAVKA, J., LEVINE, R., KOMLOSI, M. and FINK, M. EEG and task performance after heroin in post-addicts. Electroencephalography and Clinical Neurophysiology 37: 195 (1974)

To define the relation between EEG, opiate dose and. task performance, 17 detoxified heroin post-addicts received 25 mg of heroin or placebo i.v. EEGs were recorded for 10 min before and for 30 min after each injection. A continuous auditory detection task (ADT) was administered in the post-injection period. Two different tones were delivered in pairs. The subject was asked to press a key each time a special combination of tones occurred. The interval within each pair was fixed at 1 sec. and the intervals between the pairs varied between 7 and 25 sec. The frequencies and amplitudes of 5-sec segments of EEG immediately preceding the presentation of the first tone of any stimulus pair were measured by period analysis using an IBM 1800 system.

Heroin elicited a decrease of the average EEG frequency, and an increase in the delta and theta percent times. The number of omission errors for the ADT increased as the EEG frequency decreased. There was interaction between drug condition and EEG frequency: the same degree of slowing was associated with fewer omission errors after heroin than after placebo. Heroin increased the reaction time which also increased as the EEG frequencies became slower.

These results support earlier observations of relation between EEG frequency and reaction time. They also demonstrate that the relation between EEG and performance can be altered by a drug.

VOLAVKA, J., ZAKS, A., ROUBICEK, J. and FINK, M. Electrographic effects of diacetylmorphine (heroin) and naloxone in man. Neuropharmacology 9:587-593 (1970)

Sixty-three addicts were given heroin intravenously at a rate of 20-40 mg/2 cc/ 2 min, and 8-32 min later received 1-2 mg naloxone. The EEG was recorded in the pre-heroin. post-heroin and post-naloxone periods.

The early response to heroin (first 4 min after the start of the injection) was an increase in alpha amplitudes, decrease of alpha frequency and an occasional increase in alpha spindling.

The late response (5-32 min after the start of the injection) was a decrease in alpha abundance, an increase in theta and sometimes delta activities, and paroxysmal EEG activity. Two clinical seizures were seen.

The tracings returned to the pre-heroin pattern after the administra- of naloxone.

These observations of heroin and naloxone are consistent with established theories of association of EEG and behavior in man after psychoactive drugs.

VOSS, E.W., JR., BABB, J.E., METZEL, P. and WINKELHAKE, J.L. In vitro effect of d-lysergic acid diethylamide on immunoglobulin synthesis. Biochemical and Biophysical Research Communications 50(3): 950 (1973)

Rabbit anti-fluorescyl antibody producing lymphoid cells incubated in vitro with LSD do not secrete the 7S form of immunoglobulin. The low molecular weight extracellular labeled material shows no measurable anti-fluorescyl antibody activity. Results indicate that during a short incubation period LSD interferes with tryptophan incorporation into antibody protein.

VOSS, E.W., JR., METZEL, P. and WINKELHAKE, J.L. Incorporation of a lysergic acid diethylamide intermediate into antibody protein in vitro. Molecular Pharmacology 9(3): 421-425 (May, 1973)

Antibody-producing lymphoid cells incubated in vitro in the presence of /3H/ lysergic acid diethylamide (or a derivative) de novo was indicated by precipitation of labeled peptides with trichloracetic acid and by the retention of label after dialysis against denaturing agents and high concentrations of a dissociating ligand. Incorporation of /3H/ lysergic acid diethylamide by immune lymphoid cells was inhibited by puromycin and enhanced by homologous antigen.

VOSS, E.W., JR., and WINRELHAKE, J.L. Mechanisms of lysergic acid diethylamide interference with rabbit antibody biosynthesis. Proceedings of the National Academy of Sciences 71(4): 1061-1064 (April, 1974)

Lymphoid cells from hyperimmune rabbits producing antibodies to a hapten, incubated in the presence of d-lysergic acid diethyramide, continued to synthesize protein at a normal rate. Isoelectric focusing analysis of the low-molecular-weight protein secreted by the cells incubated with lysergic acid diethylamide indicated two components, with pI's of 4.9 and 5.2. Immune cells not exposed to lysergic acid diethylamide secreted only 7S IgG molecules with an average pI of approximately 7.0.

WARD, A. and TAKEMORI, A.E. Alteration of receptor sensitivity to morphine in the guinea pig ileum. Federation Proceedings 33: 502 (1974)

The ED50 of M and pA_2 of morphine-nalozone (M-N) were determined in the coaxially stimulated ileum from GP implanted s.c. with four 75 mg M pellets (MP) for 1, 2 and 3 days. Over the 3 day period, the ileum developed tolerance to the depressant effect of morphine as seen by the shift in ED50 from 2.21×10^{-7} to 2.01×10^{-6} M. Concomitantly the apparent pA_2 of M-N decreased progressively from 8.50 to 7.63. The ED50 and pA_2 returned to, control levels within 48 hr after removal of the MP. In ileums from GP treated with 6-hydroxydopamine (6-OHDA)(20 or 50 mg/kg) 6 days previously, the ED50 of M and pA_2 of M-N did not differ from control values. In ileums of GP implanted with MP for 3 days h addition to 50 mg/kg 6-OHDA injection, the developnent of tolerance and the progressive decrease in pA_2 were both partially inhibited. In ileums of 6-OHDA treated-GP the ED50 of norepinephrine (NE) was decreased compared to control. In ileums of MP-GP the ED50 of NE was increased about 4 fold whereas in ileums from 6-OHDA -treated MP-GP the increase in ED50 was slightly over 3 fold. In ileums of MP-GP the dopamine dose-response curve. only reached 50% of max. response. The data indicate that the development of tolerance in the GP ileum to the effects of M is accompanied by a qualitative change in the M receptors. The integrity of the catecholaminergic nerves does not appear to be required for the acute action of M but may be partially involved in the development of tolerance.

WASSERMAN, A. and KHAZAN, N. Effects of chronic treatment with imipramine, desipramine and trimipramine on REM sleep in the rat. The Pharmacologist 13: 255 (1971)

The various tricyclic antidepressants exhibit several dissimilarities in both pharmacologic and therapeutic profiles. In an acute study, trimipramine, unlike imipramine and desipramine, demonstrated no suppression of REM sleep in the rat (Khazan, N. and Brown, P., Life Sci. 9:279, 1970). The present study was undertaken to determine whether this characteristic would persist during chronic treatment. Groups of five rats implanted with cortical and muscle electrodes as well as i.p. cannulae were used. Administration of imipramine and desipramine at doses of both 5 and 10 mg/kg/6hr for 3-5 days resulted in a highly significant reduction (p less than 0.01) in REM time. REM sleep suppression was still evident for one to two days after drug withdrawal and was subsequently followed by a marked REM rebound. Trimipramine given chronically at equivalent doses, on the other hand, exerted essentially no REM suppressant effect (p greater than 0.05). At a higher dose level of 20 mg/kg, moreover, only relatively slight reduction (p less than 0.05) in REM time was apparent. These results suggest that chronic treatment with trimipramine, in contrast with imipramine and desipramine, exerts only minimal, if any, REM sleep suppression.

WATERS, D.H. and OKAMOTO, M. Increased central excitability in nondependent mice during chronic barbital dosing. Drug Addiction: Experimental Pharmacology, Vol. 1. Edited by J. M. Singh, L. H. Miller and H. Lal. Mount Kisco, New York: Futura Publishing Company, Inc., 1972.

WAY, E. L. Brain neurohormones in morphine tolerance and dependence. Pharmacology and the Future of Man. Proceedings of the 5th International Congress on Pharmacology, Vol. 1. San Francisco: Karger, Basel. 1973. Pp. 77-94.

WAY, E.L. Some biochemical aspects of morphine tolerance and physical dependence. Opiate Addiction: Origins and Treatment. Edited by S. Fisher and A. Freedman. Washington, D.C.: V. H. Winston and Sons, Inc., 1974.

WAY, E.L., HO, I.K. and LOH, H.H. Brain 5-hydroxytryptamine and cyclic AMP in morphine tolerance and dependence. Advances in Biochemical Psychopharmacology, Vol. 10. New York: Raven Press, 1974. Pp. 219-229.

WAY, E.L. and SETTLE, A. Cholinergic-dopaminergic interaction during morphine abstinence. Presented at the 9th International Congress on Neuropsychopharmacology, Paris, France, July, 1974.

WEI, E. Assessment of precipitated abstinence in morphine-dependent rats. Psychopharmacologia 26: 35-44 (1973)

For abstract, see Section I. Methodology of Drug Research.

WEI, E. Brain lesions attenuating "wet shake" behavior in morphine-abstinent rats. Life Sciences 12 (Part I): 385-392 (1973)

Naloxone precipitates repetitive shaking movements in morphine-dependent rats. This response, termed "wet shakes," is still present in dependent animals anesthetized with sodium pentobarbital. Transverse brain lesions, made bilaterally with an iridectomy knife in anesthetized morphine-dependent rats, completely inhibited the wet shake response to naloxone when the transection was made at the mid-collicular level. Lesions anterior to the fasciculus retroflexus did not significantly affect the wet shake response.

WEI, E. Morphine analgesia, tolerance and physical dependence in the adrenalectomized rat, British Journal of Pharmacology 47(4): 693-699 (April, 1973)

For abstract, see Section I. Methodology of Drug Research.

WEI, E. and LOH, H. Morphine physical dependence unaltered by previous dependence. on morphine. Nature 238: 396-397 (1972)

WEI, E., LOH, H.H. and WAY, E.L. Brain sites of precipitated abstinence in morphine -dependent rats. The Journal of Pharmacology and Experimental Therapeutics 185(1): 198-115 (1973)

For abstract, see Section II. Drug Chemistry and Metabolism.

WEI, E., LOH, H. H. and WAY, E.L. Neuroanatomical correlates of morphine dependence. Science 177: 616-617 (August, 1972)

For abstract, see Section I. Methodology of Drug Research.

WEI, E., TSENG, L.F., LOH, H. and WAY, E.L. Similarity of morphine abstinence signs to thermoregulatory behaviour. Nature 247: 398 (1974)

The precipitated abstinence syndrome consists of a series of behaviooral events which appear in morphine-dependent organisms after the administration of narcotic antagonists. Martin has suggested that some precipitated abstinence signs arise because an error force is generated when a narcotic antagonist resensitizes a homeostat previously altered by a narcotic. Recently, in studies on the neuroanatomical correlates of morphine withdrawal, we found that brain areas associated with the wet shake behaviour of precipitated abstinence in the rat seemed to be closely adjacent to central pathways of heat dissipation and heat gain. As morphine has complex effects on central thermoregulatory mechanisms, the possibility was considered that the generation of an error signal in central thermoregulatory systems may account for the appearance of some precipitated abstinence signs. To test this hypothesis, we investigated the effects of environmental temperature on the precipitated abstinence syndrome.

WEI, E. and WAY, E.L. Application of the pellet implantation technique for the assessment of tolerance and physical dependence in the rodent. Methods of Narcotic Research. Edited by S. Ehrenpreis and A. Neidle. New York: Marcel Dekker. Inc., 1974.

WHITE, R.P., DREW, G.W. and FINK, M. Neuropharmacological analysis of agonistic actions of cyclazocine in rabbits. Biological Psychiatry 1:217-330 (1971)

The present study was undertaken to determine the neuropharmacological effects of cyclazocine; its interaction with opiates and to contrast the profile with imipramine in rabbits. The observations support the hypothesis that cyclazocine produces agonistic effects, some resembling imipramine, independent of its ability to occupy narcotic receptors, and these effects contribute to its efficacy in the treatment of opiate dependence.

WIKLER, A., NORRELL, H. and MILLER, D. Limbic system and opioid addiction in the rat. Experimental Neurology 34(3): 543-557 (19'72)

Statistical comparisons of means in groups of morphine-dependent (or post-dependent) rats with and without bilteral lesions in the cingulum, the dorsomedial thalamic nucleus, the anterior temporal lobe (amygdaloid complex and ventral hippocampus), or the septum, and in nondependent rats with and without such lesions, revealed no significant lesion effects on specific signs of the 24-hr primary morphine-abstinence syndrome in this species: decreased water intake; increased "no-choice" drinking of a 5-mu-g/ml aqueous solution of a potent opioid (etonitazene); increased "wet dog" shake frequency; fall in colonic temperature. Lesions in the cingulum attenuated one sign of the secondary (protracted) morphine-abstinence syndrome (increased 24-hr water consumption). None of the lesions altered the suppressive effects on the primary morphine-abstinence syndrome of "no-choice" etonitazene-drinking or of intraperitoneal injection of morphine. None of the lesions prevented "relapse" of postdependent rats, as measured by comparisons of mean volumes of etonitazene (5-mu-g/ml) and water consumed in "choice" trials 9-72 days after permanent withdrawal of morphine.

WILK, S. Cerebrospinal fluid levels of MHPG in affective disorders. Nature 235(5339): 440-441 (February 25, 1972)

WILLEY, T.J., HUNT, G.M. and PETERS, M.A. Computer analysis of methadone effects on the electroencephalogram. Electroencephalography and Clinical Neurophysiology 34(7): 715 (1973)

The acute effects of intravenous administration of methadone on spontaneous brain activity were investigated in the adult cat. Bipolar electrodes for recording the EEG were placed by stereotaxic methods in subcortical and cortical brain structures. In most conditions the EEG was recorded monopolarly except in the prepyriform cortex where the electrodes straddled the superficial pyramidal cell body layer. An indwelling intravenous catheter in the external jugular vein was used for placebo and drug administration. The primary EEG was also recorded on analogue tape for computer analysis. One channel was used to obtain the EMG from neck muscles as an adjunct in defining the awake vs. asleep behavioural state prior to methadone injection.

Willey, T.J., Hunt, G.M. and Peters. M.A. continued

Analogue EEG samples from single or up to four channels were played back to the digitizing input ports on the PDP-12 computer. Frequency spectra were computed using the Fast-Fourier Transform and stored on Linc Tape. The EEG spectra consisted of 1.8 sec epochs. For visualization purposes these spectra were averaged from 2-12 times and plotted dynamically across time, using hidden-line suppression techniques to give a quasi-three dimensional representation of the EEG spectral content. Subtle frequency shifts or alterations attributed to methadone treatment were apparent from these plots. Multivariate statistical analysis was applied to the frequency spectra to ferret out significant features related to the drug-induced changes. The major effects were observed in the occipital and prepyriform cortex, with less effects observed in hippocampus, caudate nucleus and reticular formation. In general the' pattern was consistent with behavioural altering.

WILLIAMS, N.W. and CLOUET, D.H. The effect of morphine on the uptake and release of neurotransmitters by isolated synaptosomes. Proceedings of the Fifth International Congress on Pharmacology, San Francisco, California, 1972. P. 253.

WILSON, M.C. and SCHUSTER, C.R. The effects of chlorpromazine on psychomotor stimulant self-administration in the rhesus monkey. Psychopharmacologia 26: 115-126 (1972)

The effects of acute and chronic chlorpromazine treatment on psychomotor stimulant self-administration behavior in the Rhesus monkey were determined Chlorpromazine treatment significantly increased the frequency of self-administration of cocaine, pipradrol, phenmetrazine, d-amphetamine and methylphenidate. The basis of the effect was thought to either be due to an antagonism of the reinforcing effect of these compounds or an antagonism of those portions of the psychomotor stimulants which may function in limiting their self-administration.

WILSON, M.C. and SCHUSTER, C.R. The effects of stimulants and depressants on cocaine self-administration behavior in the rhesus monkey. Psychopharmacologia 31: 291-304 (1973)

The effects of acute intramuscular pretreatment with several dosages of a variety of centrally acting compounds on intravenous cocaine self-administration behavior were ascertained. Pretreatment with morphine and pentobarbital produced no change in this behavior until dosages (2.0 mg/kg and 15.0 mg/kg respectively) were administered which grossly depressed grooming, exploratory, and locomotor activity behaviors. d-Amphetamine (0.5-4.0 mg/kg) and phenmetrazine (2.0-12.0 mg/kg) pretreatment produced a dose-related decrease in cocaine self-administration. Trifluoperazine in dosages of 0.01-0.1 mg/kg increased the frequency of this behavior; whereas, higher dosages (0.2, 0.4 mg/kg) grossly depressed behavior. Imipramine (10-50 mg/kg) produced a dose-related decrease in cocaine self-administration. Potential mechanisms of these drug-behavior and drug--drug interactions are discussed.

WILSON, M.C. and SCHUSTER, C.R. Pharmacological modification of the self-administration of cocaine and SPA in the rhesus monkey. Committee on the Problems of Drug Dependence. Washington, D.C.: National Academy of Sciences, National Research Council, 1968.

In a previous report preliminary evidence was presented which showed that the frequency of self-administration of the psychomotor stimulants fencamfamin and SPA is an inverse function of the dose/injection.

In the first experiment in the present study we have replicated the previous findings with SPA and, as well, have investigated the role of unit dosage of cocaine. The data from this first experiment suggested that there exists a regulatory mechanism which controls the total amount of psychomotor stimulant drugs which monkeys will self-administer. In a second experiment we have further investigated the mechanism underlying this regulation by determining the changes in the frequency of self-administration of cocaine and SPA produced by the administration of other pharmacological agents.

WINICELHAKE, J.L., VOSS, E.W., JR. and LOPATIN, D.E. Comparative inhibitory action of d- and l-tryptophan on the effect of d-lysergic acid diethylamide in vitro. Molecular Pharmacology 10(1): 68 (1974)

The incorporation in vitro of [^{3}H]lysergic acid diethylamide into secreted protein from hyperimmune rabbit lymphoid cells was inhibited by both D- and L-tryptophan. The inhibition was specific for tryptophan isomers and analogues. On the basis of these findings a pathway was formulated to describe the preliminary steps culminating in the covalent incorporation of lysergic acid diethylamide into synthesized protein.

WINTER, B.A. and GOLDSTEIN, A. An aryl azido analogue of levorphanol for the photochemical labeling of the opiate receptor(s). Federation Proceedings 31: 528 (1972)

A radioactive analogue of levorphanol, [^{3}H]N-beta-(p-azidophenyl) ethyl-norlevorphanal (I) has been synthesized as a photochemical label for the opiate receptor site(s). Prior to photolysis, it has potent reversible opiate-like pharmacological activity in whole mice (analgesia. Straub tail, running activity) and in isolated intact guinea pig ileum (depresses twitch response to electrical stimulation). Upon photolysis of I (7.7×10^{-6}M) in the presence of BSA as a test protein for non-specific binding, radioactivity is incorporated into 1 out of 26 protein molecules. Incorporation of radioactivity upon photolysis of I (7.7×10^{-6}M) in the presence of 93,000 x g pellet of whole mouse brain homogenate also occurs. Incorporation is observed in material insoluble in H_2O and $CHCl_3$:MeOH. This incorporation is significantly but incompletely blocked by both levorphanol and dextrorphan. The implication is that non-specific binding can occur with this technique and suitable modifications are required. To determine if cellular localization occurs, radioautography of the myenteric plexus of the guinea pig ileum is being employed.

WINTER, B.A. and GOLDSTEIN, A. A photochemical affinity-labelling reagent for the opiate receptor(s). Molecular Pharmacology 6: 601-611 (1972).

For abstract, see Section II. Drug Chemistry and Metabolism.

WINTER, J.C. Behavioral effects of n, n-diethyltryptamine: Absence of antagonism by xylamidine tosylate. The Journal of Pharmacology and Experimental Therapeutics 169(1): 7 (1969)

This investigation sought todifferentiate the central and peripheral sites of action of N, N-diethyltryptamine (DET) as an aid to the interpretation of its effects on operant behavior. Rats were trained to press a bar for a food reinforcer which was delivered according to a fixed ratio schedule or a differential reinforcement of low rate schedule of reinforcement. DET, 5-hydroxytryptamine (5-HT) and 5-hydroxytryptophan (5-HTP) produced a depression or responding on the fixed ratio schedule. Cinanserin HCl antagonized the effects of all three agents. In contrast, xylamidine tosylate clearly antagonized 5-HT, was less active against 5-HTP and was without effect on DET. The response rate on the differential reinforcement of low rate schedule was also depressed by DET, 5-HT and 5-HTP. However, the DET-induced pause in bar pressing was followed by a period in which the response rate was greater than control values, The latter effect was not produced by 5-HT and 5-HTP. Rate enhancement by DET was antagonized by cinanserin HCl but was not altered by xylamidine tosylate. These results indicate that DET can be differentiated from 5-HT and 5-HTP on a behavioral basis by the use of an appropriate schedule of reinforcement and on a pharmacologic basis by the use of selective antagonists. These results support the hypothesis that DET acts on 5-HT receptors in the central nervous system to produce its behavioral effects in the rat.

WINTER, J.C. Comparison of chlordiazepoxide, methysergide and cinaserin as modifiers of punished behavior and as antagonists of n,n-dimethyltryptamine. Archives internationales de Pharmacodynamie et de Therapie 197(1): 147 (May, 1972)

Comparison of chlordiazepoxide. methysergide and cinanserin as modifiers of punished behavior and as antagonists of N, N-dimethyltryptamine. This investigation sought to test the hypothesis that tryptaminergic mechanisms are involved in the suppression of responding by punishment. Rats were trained to press a bar for food on a multiple'schedule in which one component was VI 30 (food) and the other was FR 10 (concurrent food and electric shock). Chlordiazepoxide and methysergide produced dose-related increases in both the punished and the non-punished components. Cinanserin and alpha-methyltryptamine had no rate-enhancing effects and the actions of alpha-methyltryptamine were not modified by pretreatment with the peripheral antagonist of 5-hydroxytryptamine, xylamidine tosylate. These data suggest that the ability of methysergide to increase rates of punished responding is not shared by cinanserin, a non-ergot tryptamine antagonist, and that the rate-depressant effects of alpha-methyltryptamine are not mediated by 5-hydroxytryptamine receptors in the periphery. The ability of chlordiazepoxide, methysergide, and cinaserin to antagonize the rate-depressant effects of N, N-dimethyltryptamine (DMT) was not correlated with the degree of rate enhancement produced by the administration of the drugs in the absence of DMT. These results suggest that antagonism of tryptamine is neither a necessary condition nor a sufficient condition for the enhancement of response rates suppressed by punishment.

WINTER, J. A comparison of the stimulus properties of mescaline and 2, 3, 4-trimethoxyphenylethylamine. The Journal of Pharmacology and Experimental Therapeutics 185(1):101 (1973)

This investigation sought to test the hypothesis that those pharmacologic properties which distinguish hallucinogens and non-hallucinogens in man are reflected in distinctive stimuli in the rat. Subjects were first trained on a variable interval schedule of positive reinforcement. Two drug treatments were then assigned to each animal. One treatment was the S^D, the stimulus in whose presence responses were reinforced on the variable interval schedule and the other treatment was the S-delta, the stimulus in whose presence no responses were reinforced. After 8 to 12 sessions in which the drug treatments were alternated on successive days, a punishment contingency was added, i.e., in the presence of S-delta, responses were punishment by the delivery of electric shock on a variable interval schedule. Approximately every fourth session was designated a test session and responses were neither reinforced nor punished during the first five, minutes of these sessions. In this way the efficacy of the drug treatments as discriminative stimuli was determined. It was first established, in two separate groups of rats, that mescaline, when paired with saline and 2,3,4-trimethoxyphenylethylamine (2,3,4-TMPEA). when paired with saline, can be discriminative stimuli. In a third group, equivalent doses of mescaline and 2, 3, 4-TMPEA were compared directly. If we assume that 2, 3, 4-TMPEA is without hallucinogenic activity, the hypothesis predicts that mescaline and 2, 3, 4-TMPEA will be discriminable in the rat. No evidence of discriminated responding was obtained. The present data fail to support the hypothesis that these different pharmacologic properties of hallucinogens and non-hallucinogens in man are reflected in distinctive stimuli in the rat.

WINTER, J.C. Hallucinogens as discriminative stimuli. Federation Proceedings 33(7):1825 (July, 1974)

HalIucinogens have been known to man for thousands of years and scientific methods have been applied to the study of their effects since the latter part of the last century. However, attempts to establish the pharmacologic mechanisms underlying the actions of these drugs have been hampered, in man, by ethical constraints on the type of experiments undertaken and, in animals, by the absence of an adequate model of hallucination. The work described here represents a preliminary attempt to test the hypothesis that those pharmacologic properties which serve to distinguish hallucinogens and nonhallucinogens in man are reflected in distinctive stimuli in infrahuman species. Operant behavior which is reinforced only in the presence of a specified stimulus soon occurs with greater frequency in the presence of the stimulus than in its absence and the behavior is then said to be under the control of the stimulus. In addition to well-known sensory stimuli, it has been known for some time that a drug may serve as a discriminative stimulus. In this report, a general method is presented for the comparison of the stimulus properties of pharmacologic agents and the method is illustrated by a study of mescaline, its structural isomer, 2, 3, 4-trimethoxyphenylethylamine, and 3, 4-dimethoxyphsnylethylamine (DMPEA).

WINTER, J.C. Tolerance to a behavioral effect of lysergic acid diethylamide and cross-tolerance to mescaline in the rat: Absence of a metabolic component. The Journal of Pharmacology and Experimental Therapeutics 178(3): 625-630 (1971)

For abstract, see Section II. Drug Chemistry and Metabolism.

WINTER, J.C. Xylamidine tosylate: Differential antagonism of the hypothermic effects of n, n-dimethyltryptamine, bufotenine, and 5-methoxytryptamine. Archives internationales de Pharmacodynamie et de Therapie 198(1): 61 (1972)

The effect of pretreatment with a fixed dose of xylamidine tosylate on the hypothermia produced in rats by N, N-dimethyltryptamine (DMT), bufotenine, and 5-methoxytryptamine was determined. Such pretreatment had little effect on DMT-induced hypothermia but the effects of bufotenine and 5-methoxytryptamine were antagonized. Despite the hallucinogenic properties sometimes attributed to bufotenine, it may reasonably be assumed that, of the three compounds, only DMT enters the central nervous system of the rat in significant amounts. Therefore, the present results are in agreement with the hypothesis that xylamidine acts selectively to block the peripheral component of the actions of tryptaminergic agents.

WOLPERT, A., WHITE, L., DANA, L., SUGERMAN, A.A., ARENGO, A.D., SIMPSON, G. M., BISHOP, M.P. and GALLANT, D. M. Clinical pharmacological trial of loxapine succinate. Journal of Clinical Pharmacology 10(3): 175-181 (May-June, 1970)

In an open study loxapine succinate was given to 44 subjects in four different Early Clinical Evaluation Units. The results of the studies were remarkably consistent and all investigators agreed on the activity of this preparation. This was confirmed by the nurses in all four units and received support from the BPRS in three of the units.

A dose range of 40 to 200 mg was employed, but a suggested dose range of 40 to 100 mg was put forward. Side effects consisted of drowsiness, hypotension (one subject), and extrapyramidal disorders. These latter were similar to those seen with other compounds and did not necessitate withdrawal of any subject from the trial. It was concluded by all investigators that 1oxapine possessed neuroleptic properties. None of the four trials revealed significant toxicity.

WURSTER, N., ELSBACH, P., RAND, J. and SIMON, E.J. Effects of levorphanol on phospholipid metabolism and composition in Escherichia coli. Biochimica et Biophysica Acta 248: 282-292 (1971)

The effects of growth inhibitory concentrations of the morphine analogue levorphanol on the metabolism and composition of membrane phospholipids were investigated in Escherichia coli.

Incorporation of radioactive precursors into the total lipid fraction is reduced.

During incubation with levorphanol there is a gradual rise in the proportion of radioactivity incorporated into cardiolipin, from 5% (untreated) to 55-70% after 60 min. In addition to the more rapid labeling of cardiolipin there is evidence for reduced breakdown of cardiolipin in the presence of levorphanol.

The incorporation of precursors into phosphatidyl ethanolamine is markedly reduced. The turnover of phosphatidyl glycerol is accelerated and phosphatidyl ethanolamine, normally stable, exhibits turnover in the presence of levorphanol.

After 1 h incubation with levorphanol the relative amounts of individual phospbolipids, determined as phospholipid phosphorus, are 45% phosphatidyl ethanolamine, 10% phosphatidyl glycerol and 45% cardiolipin, as compared to 68% phosphatidyl ethanolamine, 25% phosphatidyl glycerol and 7% cardiolipin in untreated bacteria.

In drug-free medium the phospholipid labeling pattern of cells labeled in the presence of levorphanol slowly reverts towards normal.

Possible relationships between the observed alterations in phospholipid metabolism and composition and the effects of levorphanol on transport and on ribosomal RNA synthesis are discussed.

WURSTBR, N., ELSBACH, P., SIMON. E.J., PETTIS, P. and LEBOW, S. The effects of morphine analogue levorphanol on leukocytes. Journal of Clinical Investigations 50(5): 1091 (May, 1971)

Studies on bacteria have suggested that morphine-like drugs have effects on the cell membrane. To determine the effect of this class of drugs on a mammalian cell, we selected the rabbit peritoneal exudate granulocyte. which undergoes striking membrane changes during phagocytosis. We examined the effect in vitro of the morphine analogue, levorphanol on phagocytosis and metabolism by granulocytes incubated with and without polystyrene particles or live Escherichia coli. Levorphanol (1 or 2 mmoles/liter) decreased: (a) acylation of lysolecithin or lysophosphatidylethanolamine in the medium (which is stimulated about two-fold during phagocytosis) both at rest (40%) and during phagocytosis (60%); (b) uptake of latex particles and Escherichia coli, as judged by electron microscopy; (c) killing of live Escherichia coli (10-fold); (d) $^{14}CO_2$ production from glucose-1-^{14}C during phagocytosis by at least 80%; (e) K^+ content of granulcocytes (35%); (f) oxidation of linoleate-1-^{14}C by 50%, and its incorporation into triglyceride, by more than 80%. However, levorphanol stimulated 2 to 3-fold the incorporation of linoleate-1-^{14}C into several phospholipids. Glucose uptake, lactate production, and adenosine triphosphate (ATP) content are not affected by the drug. Thus, levorphanol does not appear to exert its effects through generalized metabolic suppression.

Removal of levorphanol by twice resuspending the granulocytes completely reverses all inhibition.

In line with observations on bacteria, it appears that the complex effects of levorphanol on granulocytes may be due at least in part to an effect of the cell membrane.

YAGEN, B. and MECHOULAM, R. Stereospecific cyclizations and isomerizations of cannabichromene and related cannabinoids. Tetrahedron Letters 60: 5353 (1969)

YAGIELA, J.A., McCARTHY, K.D. and GIBB, J.W. The effect of hypothermic doses of 1-delta-9-tetrahydrocannabinol on biogenic amine metabolism in selected parts of the rat brain. Life Sciences 14: 2367-2378 (1974)

Hypothalamic and brainstem biogenic amine metabolism was investigated in rats following the administration of hypothermic doses of l-delta-9-tetrahydrocannabinol (THC). The dose-dependent fall in body temperature induced by THC was both rapid in onset and prolonged in duration. The disruption in thermoregulation, however, was unaccompanied by any observed alteration in the concentration or turnover rate of 5-hydroxytryptamine (5-HT) in the brain tissues studied. Norepincphrine (NE) was also unchanged, with the exception of a reduction in the amounts of brainstem NE 30 min after the administration of 50 mg/kg THC. These observations indicate that the hypothermic effect of THC is not mediated by changes in brain 5-HT of NE metabolism.

YAMAMURA, H.I. and HORITA, A. Effect of propranolol on the blockade of alpha adrenergic receptors. The Journal of Pharmacology and Experimental Therapeutics 164(1): 82 (1968)

Previous studies from this laboratory have demonstrated the antagonism of various alpha blockers by the beta blocking agent, dichloroisoproterenol. eIn the present studies, the alpha responses of agents possessing both alpha and beta adrenergic properties (epinephrine and norepinephrine) were antagonized by phenoxybenzamine and exhibited partial recovery after subsequent administration of propranolol. However, the alpha responses of agents possessing only an alpha stimulatory property (methoxamine and oxymetazoline) were not restored upon subsequent administration of propranolol. It was also shown that, even after the antagonism of phenoxybenzamine by propranolol, the phenoxybenzamine -induced blockade reappeared after the effects of propranolol had dissipated. These data therefore demonstrate that only the agonist possessing both alpha and beta activities can undergo the reversal and recovery. It is postulated that this antagonism does not involve a displacement mechanism of phenoxybenzamine by propranolol but is associated with the unmasking of residual alpha receptor sites which were not blocked by the original dose of phenoxybenzamine.

YAMAMURA, H.I. and HORITA, A.A further study of the effect of propranolol on the blockade of alpha adrenergic receptors. European Journal of Pharmacology 7: 258-263 (1969)

The results reported herein have shown that the pressor responses of adrenergic agonists possessing only an alpha stimulatory property (oxymetazoline) were not restored to significant values after phenoxybenzamine and propranolol blockade. However, when the alpha agonistic property of oxymetazoline was combined with the beta stimulatory property of isoproterenol, significant recovery of the pressor response was noted after alpha and beta blockade. The results indicated that the pressor activity of the oxymetazoline plus isoproterenol mixture seemed to mimic the actions of a known alpha and beta agonist: epinephrine. The data also showed that time affected the antagonism of phenoxybenzamine by propranolol and of significance was the consistent finding that the phenoxybenzamine-induced alpha blockade reappeared after the effects of propranolol had worn off. These data provide further proof that only the agonists possessing both alpha and beta stimulatory activities can undergo the reversal after alpha receptor blockade. It is therefore postulated that the antagonism between alpha and beta blocking agents is associated with the activation of residual alpha receptors not blocked by phenoxybenzamine rather than the hypothesis of competitive displacement of phenoxybenzamine by propranolol.

YAMAMURA, H.I. and SNYDER, S.H. High affinity transport of choline into synaptosomes of rat brain. Journal of Neurochemistry 21: 1355-1374 (1973)

The accumulation of (^{3}H)choline into synaptosome-enriched homogenates of rat corpus striatum, cerebral cortex and cerebellum was studied at (^{3}H)choline concentrations varying from 0. 5 to 100 mu-M. The accumulation of (^{3}H)choline in these brain regions was saturable. Kinetic analysis of the accumulation of the radiolabel was performed by double-reciprocal plots and by least squares iterative fitting of a substrate-velocity curve to the data. With both of these techniques, the data were best satisfied by two transport components, a high affinity uptake system with K_m values of 1.4 mu-M (corpus striatum), and 3.1 mu-M (cerebral cortex) and a low affinity uptake system with respective K_m values of 93 and 33 mu-M for these two brain regions. In the cerebellum choline was accumulated only by the low affinity

Yamamura, H.I. and Snyder, S.H. continued
system. When striatal homogenates were fractionated further into synaptosomes and mitochondria and incubated with varying concentrations of (^{3}H)choline, the high affinity component of choline uptake was localized to the synaptosomal fraction. The high affinity uplake system required sodium, was sensitive to various metabolic inhibitors and was associated with considerable formation of (^{3}H)acetylcholine. The low affinity uptake system was much less dependent on sodium, and was not associated with a marked degree of (^{3}H)acetylcholine formation. Hemicholinium-3 and acetylcholine were potent inhibitors of the high affinity uptake system. A variety of evidence suggests that the high affinity transport represents a selective accumulation of choline by cholinergic neurons, while the low affinity uptake system has some less specific function.

YANAGITA, T. Development of tolerance and physical dependence to barbiturates in rhesus monkeys. Committee on Problems of Drug Dependence, Washington, D.C.: National Academy of Sciences, National Research Council. 1968. P. 5618.

YARBROUGH, G.G., BUXRAUM, D.M. and SANDERS-BUSH, E. Increased serotonin turnover in acutely morphine treated mice. Biochemical Pharmacology 21(Part3): 2667-2670 (1972)

YARYURA-TOBIAS, J.A., DIAMOND, B. and MERLIS, S. The action of L-dopa on schizophrenic patients (a preliminary report) Current Therapeutic Research 12(8): 528-531 (August, 1970)

YARYURA-TOBIAS, J.A., WHITE, L., WOLPERT, A., DANA, L. and MERLIS, S. Clinical study of the possible antidepressant action of NC-0687. Current Therapeutic Research 11(9): 574-576 (September, 1969)

NC-0687 is a new chemical structure which is defined as 4-phenyl-4(4-N-methyl-delta^3 piperidine)-3 oxatricyclo (4.2.1.0^{2,5}) Nonane. It main action as observed in several animal species is that of a strong antidepressant agent. 'By comparison, it appears to have activity one and a half times that of imipramine. However, twice as much NC-0687 is required to prevent the depression caused by tetrabenazine. This drug has a marked anticholinergic effect and a mild anorexic action. It also causes a potentiation of the pressor response to injected norepinephrine. In the dog, hepatoxicity with enlargement of the liver has been reported. A study of human dose range and toxicity indicated several marked side effects at the 30 mg daily level. In order of frequency, the side effects were: myalgia, blurred vision, dry mouth, dizziness, nausea, drowsiness, headache, euphoria, urinary difficulty, breathing difficulty and testicular soreness. At dosage below 30 mg daily, apparently no untoward side effects were encountered. An open study to determine possible antidepressant action of NC-0687 was undertaken.

YARYURA-TOBIAS, J.A., WOLPERT, A., DANA, L. and MERLIS, S. Action of L-dopa in drug induced extrapyramidalism. Diseases of the Nervous System 31: 60 (1970)

YARYURA-TOBIAS, J.A., WOLPERT, A., WHITE, L., AGOLA, P. and MERLIS, S. A clinical evaluation of clopenthixol. Current Therapeutic Research 12(5): 271-279 (May, 1970)

YEH, S.Y. and MITCHELL, C.L. Potentiation and reduction on the analgesia of morphine in the rat by pargyline. The Journal of Pharmacology and Experimental Therapeutics 179: 642-651 (1971)

The effect of pargyline on the analgesia of morphine in rats has been investigated. The analgesia in the animals receiving morphine one or four hours after an acute injection of pargyline was increased significantly one and two hours after morphine as compared to those receiving saline followed by morphine. In contrast, 24 hours after an acute injection of pargyline, there was a tendency for a decrease in the analgesic effect of morphine. The concentration of free morphine in the brain tissue of rats treated acutely with pargyline four hours prior to the injection of morphine was significantly higher than that of the saline control animals at one and two hours after morphine. In contrast to the results obtained after acute administration of pargyline, chronic administration significantly decreased the analgesic effect of morphine one-half hour after its injection. Experiments in vitro demonstrated that pagyline in a concentration as low as 1.0×10^{-4}M inhibits morphine glucuonide formation by about 50% in liver microsomes from normal rats. The liver microsomal glucuronyl transferase activity of rats treated with pargyline daily for seven or eight days was increased about 40% of that of the saline control rats. Induction of glucuronyl transferase activity may explain the fact that adverse reactions seldom occur with morphine in patients treated chronically with monoamine oxidase inhibitors.

YOKEL, R.A. and PICKENS, R. Intravenous self-administration of dextro and levo isomer of amphetamine and methamphetamine by rats. The Pharmacologist 13(2): 281 (1971)

The dextro isomers of amphetamine and methamphenamine have been shown to be intravenously self-administered by rats. In the present experiments, the levo isomers of amphetamine and methamphetamine were found to maintain self-administration originally established using the dextro-isomers of both compounds. Drug naive animals were also found to initiate responding for the levo-isomers of both compounds. With all 4 isomers, uniform intervals separated each drug infusion, with the length of the interval inversely related to drug dose, suggesting autotitration of drug effect. Stereotypic head and body movements were seen at all infusion doses. Intake of levo-amphetamine (4.3 mg/kg/hr) was about 3 times that of dextro-amphetamine (1.3 mg/kg/hr) using infusion doses of .25-1 mg/kg. Intake of levo-methamphetamine (10.8 mg/kg/hr) was about 5 times that of dextro-methamphetamine (2.2 mg/kg/hr) using infusion doses of 1-2. 5 mg/kg. Slightly more drug per hour was taken at the higher infusion doses. The dextro and levo intake comparisons agree in magnitude with other reported measures of the central activity of amphetamine, and methamphetamine. indicating that the autotitration phenomena with these drugs is mediated centrally rather than peripherally.

ZAKS, A.M., BRUNER, A., FINK, M. and FREEDMAN, A. M. Intravenous diacetylmorphine (heroin) in studies of opiate dependence. Diseases of the Nervous System 30(Supplement): 89-92 (1969)

ZAKS, A., FINK, M. and FREEDMAN, A.M. Duration of methadone induced cross-tolerance to heroin. British Journal of the Addictions 66: 205-208 (1971)

ZAKS, A., FINK, M. and FREEDMAN, A.M. Levo-methadyl in maintenance treatment of opiate dependence. Journal of the American Medical Association 220(6): 811 (May, 1972)

In a comparison of methadone hydrochloride and levomethadyl acetate (l-alpha-acetylmethadol), 20 male, opiate-dependent subjects were assigned at random to either regimen. Methadone-treated subjects received methadone hydrochloride, 100 mg daily. Levomethadyl patients received doses on Monday, Wednesday, and Friday only. Four received low doses (30 to 50 mg), and six received high doses (80 mg). Both regimens were well tolerated. At six months, eight of ten methadone-treated patients and eight of nine levomethadyl-treated patients were undergoing treatment. In patient acceptance, withdrawal symptoms, response to heroin challenges, and number of positive results for urine tests measured for morphine, the two groups were equivalent. Levomethadyl acetate, 80 mg administered three times per week, is equivalent to daily administration of 100 mg of methadone hydrochloride. Large-scale clinical trials of levomethadyl acetate are suggested.

ZAKS, A., JONES, T., FINK, M. and FREEDMAN, A.M. Naloxone treatment of opiate dependence. Journal of the American Medical Association 215(13): 2108 (March, 1971)

The duration of action of naloxone hydrochloride, a narcotic antagonist, was extended by increasing doses in nine male volunteers. Blockade against intravenously administered heroin challenges was measured. A daily dose of 2.4 gm of naloxone hydrochloride elicited blockade to 25 mg of heroin and 3.0 gm extended blockade to 59 mg of heroin both for 24 hours. No toxic symptoms occurred in nine weeks of naloxone administration. In order to use antagonists in the prophylaxis of opiate dependence, a long-acting, parenterally administered Formulation must be developed.

ZIMMERMANN, E., BRANCH, B., TAYLOR, A., YOUNG, J. and PANG, C. Dexamethasone inhibition of morphine-induced release of ACTH in male rats. Proceedings of the 58th Annual Meeting of the Federation of American Societies for Experimental Biology, Atlantic City, New Jersey, April, 1974.

Morphine (M) stimulation of pituitary-adrenal function in the rat is blocked by prior administration of dexamethasone (Dex) (PSEDM 143: 1224, 1973). To determine the dose requirements for this blockade adult male Sprague-Dawley rats were given saline (S) or Dex subcutaneously followed 2 h later by M (30 mg/kg, i.p.). One h after M injection, plasma levels of corticosterone (B) were elevated (p less than 0. 03) in S-pretreated controls and depressed in rats pretreated with 20 (p less than 0.05) or 100 (p less than 0.01). but not with 5 (p greater than 0.05). mu-g/kg Dex. Temporal studies revealed elevated (p less than 0.01) B levels 30 and 60 min, but not 12 0 min, after injection of M while B levels in Dex (100 mu-g/kg) pretreated rats were depressed (p less than 0.01) at each of these times. When given either 0, 1, 2, 6 h, but not 12 or 21 h, before M, Dex (103 mu-g/kg) completely blocked the B response to M. When given 30 min after M. 100 mu-g/kg Dex caused partial (p less than 0.05) and 40 mu-g/kg Dex caused complete (p less than 0.01) suppression of the B response to M. Unlike 400 mu-g/kg Dex, equimolar doses of cortisone, cortisol and desoxycorticosterone failed to suppress the B response to M. These findings indicate that Dex causes temporary dose-dependent inhibition of M-induced release of ACTH in the rat, presumably involving neural effects of these two centrally-active agents.

ZIMMERMANN, E., BRANCH, B., TAYLOR, A.N., YOUNG, J. and PANG, C.N. Long-lasting effects of prepuberal administration of morphine in adult rats. Narcotics and the Hypothalamus. Edited by E. Zimmermann and R. George. New York: Raven Press, 1974.

To study effects of prepuberal administration of morphine on body growth and pituitary-adrenal function, newborn Sprague-Dawley male and female rats were given subcutaneous saline or morphine (to 8 mg/kg twice daily) from 1 to 21 days of age. Compared with controls, body weights of morphine-treated animals were reduced (p less than 0.01) by day 7 and remained significantly depressed for 105 days in females, and for at least 120 days in males. Puberty (vaginal or preputial opening) occurred simultaneously in morphine- and saline-treated rats of each sex. On day 56, all groups showed normal diurnal patterns of non-stress levels of plasma corticosterone. Compared with non-stressed controls on day 72, morphine-treated male and female rats showed intact corticosterone responses to ether stress. However, female but not male rats showed reduced (p less than 0.05) corticosterone responses to morphine (20 or 40 mg/kg). Similarly, on day 80, morphine-treated . females showed reduced (p less than 0.05) analgesic response to morphine (10 mg/kg), tested using the hot -plate technique, while the males showed an equivocal response. Finally, on day 92, morphine-treated females but not female controls or males showed increased (p less than 0.05) plasma corticosterone levels 30 *min* after injection of naloxone (5 mg/kg). The persistence of growth deficit, tolerance to morphine, and sensitivity to naloxone suggests that exposure of the immature female rat to morphine results in prolonged, possibly permanent, morphine-specific alteration of neuroendocrine and nociceptive brain mechanisms.

ZIMMERMANN, E. and CRITCHLOW, V. Inhibition of morphine-induced pituitary-adrenal activation by dexamethasone in the female rat. Proceedings of the Society for Experimental Biology and Medicine 140(4): 1224 (September, 1973)

It is well established that morphine sulfate (MS) markedly stimulates pituitary-adrenal function in the unanesthetized rat. Recently, Kokka et. al. reported complete inhibition of this response to MS by prior administration of a large dose (600 mu-g/kg) of the synthetic corticosteroid, dexamethasone (Dex). The present study was performed to examine the sensitivity of MS-induced pituitary-adrenal activation to the inhibitory action of relatively low doses of Dex in the female rat.

ZIMMERMANN, E., GISPEN, W.H., MARKS, B.H. and DeWIED, D., editors. Drug Effects on Neuroendocrine Regulations. Progress in Brain Research, Vol. 39. New York: Elsevier Press. 1973.

ZIMMERMANN, E., YOUNG, J., BRANCH, B., TAYLOR, A.N. and PANG, C.N. Long-lasting effects of prepuberal administration of morphine in female rats. Narcotics and the Hypothalamus. Edited by E. Zimmermann and R. George. Kroc Foundation Symposium No. 2, 1974.

To study effects of prepuberal administration of morphine on body growth and pituitary-adrenal function newborn Sprague-Dawley female rats were given subcutaneous saline (S) or morphine (M) (to 8 mg/kg, b.i.d.) from 1-21 days of age. Compared with controls body weights of M-treated animals were reduced (p less than 0.01) by Day 7 and remained significantly depressed for approximately 120 days. Puberty (vaginal opening) occurred simultaneously in M- and S-treated rats on Days 36 + 2. On Day 56, both groups showed comparable diurnal patterns of non-stress levels of plasma corticosterone (B). Compared with controls on Day 72, M-treated rats showed intact B responses to ether stress but reduced (p less than 0.05) B responses to M (20 or 40 mg/kg). Similarly, on Day 80, M-treated rats showed reduced (p less than 0.05) analgetic response to M (10 mg/kg) using the hot-plate test. Finally, on Day 92, M-treated rats, but not controls, showed increased (p less than 0.05) plasma B levels 30 min after injection of naloxone (5 mg/kg). Persistence of growth deficit, tolerance to M, and sensitivity to naloxone suggests that exposure of the immature female rat to morphine results in prolonged, M-specific alteration of neuroendocrine and noniceptive brain mechanisms.

ZIMMERMANN, E., YOUNG, J., BRANCH, B., TAYLOR, A.N., PANG, C.N. and SAWYER, C.H. Long lasting effects of prepuberal administration of morphine in female rats. Journal of Steroid Bipchemistry 5: 387 (1974)

To study effects of prepuberal administration of morphine on body growth and' pituitary-adrenal function, newborn Sprague-Dawley female rats were given subcutaneous saline (S) or morphine (M) (to 8 mg/kg. b.i.d.) from 1-21 days of age. Compared with controls, body weights of M-treated animals were reduced (p less than 0.01) by day 7 and remained significantly depressed for approximately 123 days. Puberty (vaginal opening) occurred simultaneously in M- and S-treated rats on days 35 + 2. On day 56, both groups showed comparable diurnal patterns of non-stress levels of plasma corticosterone (B). Compared with control on day 72, M-treated rats showed intact B responses to ether stress, but reduced (p less than 0.05) B responses to M (23 or 40 mg/kg). Similarly, on day 80, M-treated rats showed reduced (p less than 0.05) analgetic response to M (10 mg/kg) using the hot-plate test. Finally, on day 92, M-treated rats, but not controls, showed increased (p less than 0.05) plasma B levels 30 min after injection of naloxone (5 mg/kg). Persistence of growth deficit, tolerance to M, and sensitivity to naloxone suggest that exposure of the, immature female rat to morphine results in prolonged M-specific alteration of neuroendocrine and nociceptive brain mechanisms.

ZUCKER-FRANKLIN, D., ELSBACH, P. and SIMON, E.J. The effect of the morphine analog levorphanol on phagocytosing leukocytes. Laboratory Investigation 25(5): 415 (1971)

It has been reported recently that the morphine-like drug levorphanol inhibits several biochemical reactions of polymorphonuclear leukocytes both at rest and during phagocytosis. The drug also reduces the bactericidal capacity of the cells. Electron microscope studies were carried out to determine whether the metabolic effects produced by this compound were reflected by alterations in the morphologic aspects of the phagocytic process. Accordingly, human and rabbit granulocytes were incubated with latex particles or Escherichia coli in the presence and absence of levorphanol. Levorphanol inhibited the uptake of latex particles by leukocytes by 80 to 90 percent. Phagocytosis of E. coli was less consistently inhibited, the reduction ranging from 20 to 80 per cent. When E. coli were the particles ingested by the cells, it was also evident that degranulation had been reduced by the drug. The effect of levorphanol was readily reversed by removal of the compound from the medium. Although the exact site(s) of action of levorphanol remain(s) to be established, the compound may be a useful agent in the analysis of various aspects of leukocyte function.

Indexes