plasma levels in patients receiving CPZ and other forms of therapy. These studies may help to resolve the problem of the wide variation in clinical response to CPZ therapy and the variation in CPZ plasma levels among patients on a given dose.

Subjects: Psychiatric inpatients participate in this research.

Method: Analysis of blood samples and psychiatric assessment are carried out twice or once a week for 4-6 weeks. A gas-liquid chromatographic method is used to determine CPZ plasma levels. Clinical status is established via standardized psychiatric rating scales and other measures of performance and behavior. In a different series of studies, the investigator attempts to determine: 1) if plasma CPZ levels would show some correlation with clinical improvement, and 2) factors that affect plasma CPZ levels, i.e., a) dose, b) dosing interval, and c) multiple drug prescribing.

Results: The plasma CPZ levels of 50 acutely psychotic inpatients were measured by gas-liquid chromatography, and the clinical progress of 29 acute patients was monitored by the Brief Psychiatric Rating Scale once a week for 4-6 weeks.

It was shown that CPZ plasma levels of 50-300 ng/ml were generally associated with clinical improvement, especially in paranoid behavior and thought disorder. This range was found to be best attained by doses of 400-800 mg/day; higher doses produced untoward side effects. A single h.s. (*hora somni*) dose of 400-800 mg. was found to produce steady states of plasma CPZ equal to, or better than, those achieved by a multiple dosage schedule of the same total daily dose in the same patients. Trihexyphenidyl (Artane), a commonly used antiparkinsonian agent, was found to decrease plasma CPZ significantly. The interaction appeared to be in the absorption stage. Finally, patients who failed to attain adequate plasma CPZ levels despite doses of 400-1000 mg/day were found to be receiving lithium throughout the study period, with a diagnosis of manic-depressive (manic) and schizo-affective (excited). The lithium and CPZ interaction is currently being studied.

Magnetic Circular Dichroism of Substituted Indoles

Investigator: Donald D. Shillady
Virginia Commonwealth University
Richmond, Virginia

Purpose: A highly sensitive spectrometer is being developed to measure circular dichroism induced by a powerful magnetic field. This technique is to be used in analytical detection procedures and monitoring in enzyme kinetic studies of biochemicals and psychopharmacological agents containing the indole moiety. Magnetic circular dichroism (MCD) offers a number of advantages over other techniques; e.g., no fractionation is necessary and immediate direct measurements can be made speedily and economically.

Subjects: Cockroaches and white rats are used in some of the detection studies.

Method: The investigator measures the time-averaged MCD spectra of serotonin and its biosynthesis from L-tryptophan via 5-hydroxytryptophan, followed by degradation to 5-hydroxyindole acetaldehyde and 5-hydroxyindole acetic acid. The kinetics of these enzymic reactions are studied *in vitro* by noting changes in the MCD spectra. A minicomputer is interfaced to perform time-averaged scanning to about one Ångstrom unit resolution. In studies with related compounds such as psilocyn and 5-hydroxytryptophol, the investigator analyses the electronic effects of chemical substitution of the parent compound as manifested in the MCD spectra. He uses fluorescence and ultraviolet spectroscopy to check the analytical results and augment the electronic interpretations.

Results: This study is in the initial stages.

Effects of Psychotropic Drugs on Brain Nuclear RNA

Investigator: Steven J. Smith
Pennsylvania State University
University Park, Pennsylvania

Purpose: The investigator is studying the ties between nuclear RNA metabolism in specific brain subregions and the behavioral effects of various psychotropic agents. In the first part of the study, alterations of nuclear RNA metabolism are examined during states of inhibition of ribosomal RNA synthesis and processing and during acute and chronic treatment with morphine, phenobarbital, amphetamine, lysergic acid diethylamide, delta^9 -tetrahydrocannabinol, and chlorpromazine. In the second part of the study, alterations in nuclear RNA metabolism related to growth and development are investigated.

Subjects: Male rats are used in these experiments.

Method: In the first part of the study criteria are established for identification of brain nuclei of different cell types. Rapidly labeled RNA is extracted from nuclei and analyzed by acrylamide-agarose gel electrophoresis to obtain 45S RNA, the ribosomal precursor. Various physicochemical parameters of ribosomal RNA metabolism

are examined, including RNA polymerase activity of aggregate and solubilized enzyme; stability of newly formed RNA; and electrophoretic mobility, turnover, and base composition of the RNA. The second part of the study is carried out with 7- to 9-day-old, 20-day-old, and 90-day-old animals. Electron microscopy is used as an index of purity of nuclei and to study the morphology of brain nuclear subfractions during normal rat growth and during treatment by the agents applied in the first part of the study.

Results: This research is in the initial stages.

Preclinical Studies of Rubidium in Affective Illness

Investigator: Jon M. Stolk
Dartmouth Medical School
Hanover,
New Hampshire

Purpose: Rubidium chloride, an alkali metal salt, increases the turnover of brain norepinephrine stores and facilitates expression of several types of behavior, a spectrum of activity that suggests rubidium might be of value as a clinical antidepressant. In the present study, the investigator is examining rubidium's effects on catecholamine physiology and behavior and the drug's potential nephrotoxicity.

Subjects: Rats and dogs are used in the experiments.

Method: The investigator analyzes dosage and temporal variables of rubidium's effects on brain norepinephrine synthesis and turnover using radiolabeled tyrosine and dopamine as norepinephrine precursors. The drug's impact on shuttle box avoidance behavior and on free operant avoidance performance is compared with the effects of known antidepressant agents. Studies of clearance, transport, and reabsorption are designed to evaluate renal function. Comprehensive histopathological examinations are conducted to follow up the appearance of any renal abnormalities.

Results: Recently, the investigator reported that rubidium caused an increase in norepinephrine turnover and increased synthesis of norepinephrine from tyrosine. Investigations of norepinephrine metabolism in brain failed to replicate the findings of an earlier study showing enhancement of normetanephrine formation. However, a study of acute dose-response relationships indicated that norepinephrine metabolism may be decreased by rubidium chloride treatment under certain conditions. The acute decrease in metabolism appeared to correlate well with the acute effects of rubidium on rat electroencephalogram (EEG) activity, which showed increased voltage content and increased rate of spindle events. After subacute rubidium dosing, the EEG pattern reversed, showing the development of increased desynchronous activity by the tenth daily dose of rubidium. The latter effect was consistent with turnover studies and with the proposed use of this drug as an antidepressant. Subacute toxicity studies in dogs revealed no major gross pathological changes but indicated definite areas of concern which require further detailed investigation before human usage could be considered.

Brain Dopamine-Beta-Hydroxylase Regulation and Behavior

Investigator: Jon M. Stolk
Dartmouth Medical School
Hanover,
New Hampshire

Purpose: Recent research indicates that schizophrenics may be deficient in dopamine-beta-hydroxylase (DBH), an enzyme involved in norepinephrine synthesis. The investigator is conducting animal studies of the effects of various stresses and behavioral modifications on changes in brain levels of this enzyme in a search for clues to mental illness in man.

Subjects: Rats and rabbits are used in the experiments.

Method: Employing an *in vivo* method for estimating brain enzyme activity, the investigator studies the DBH effects of cold stress, electric footshock, electroconvulsive shock, immobilization, and social stress. Particular attention is paid to the regulatory mechanisms controlling *in vivo* enzyme activity in the face of these stresses. By comparing brain enzyme activity *in vivo* with that estimated by standard *in vitro* techniques, the investigator differentiates between altered activity of existing enzyme protein and adaptive changes in enzyme protein level. The stimulus specificity and temporal patterns of altered DBH activity are also explored. The investigator attempts to show how an animal's response to a given stimulus modifies the effect of that stimulus on mechanisms controlling brain DBH activity and protein. An effort is made to document potential alterations that might possibly occur in man.

Results: Recent footshock studies indicated that acute changes in *in vivo* DBH activity were dependent upon shock intensity. Brain stem (medulla-pons) DBH activity *in vivo* decreased by 25 percent immediately following exposure to a single 10-minute shock session at a shock intensity of 1.8 milliamperes (ma.), shock intensity of 1.3 ma. evoked no change, and neither shock intensity caused