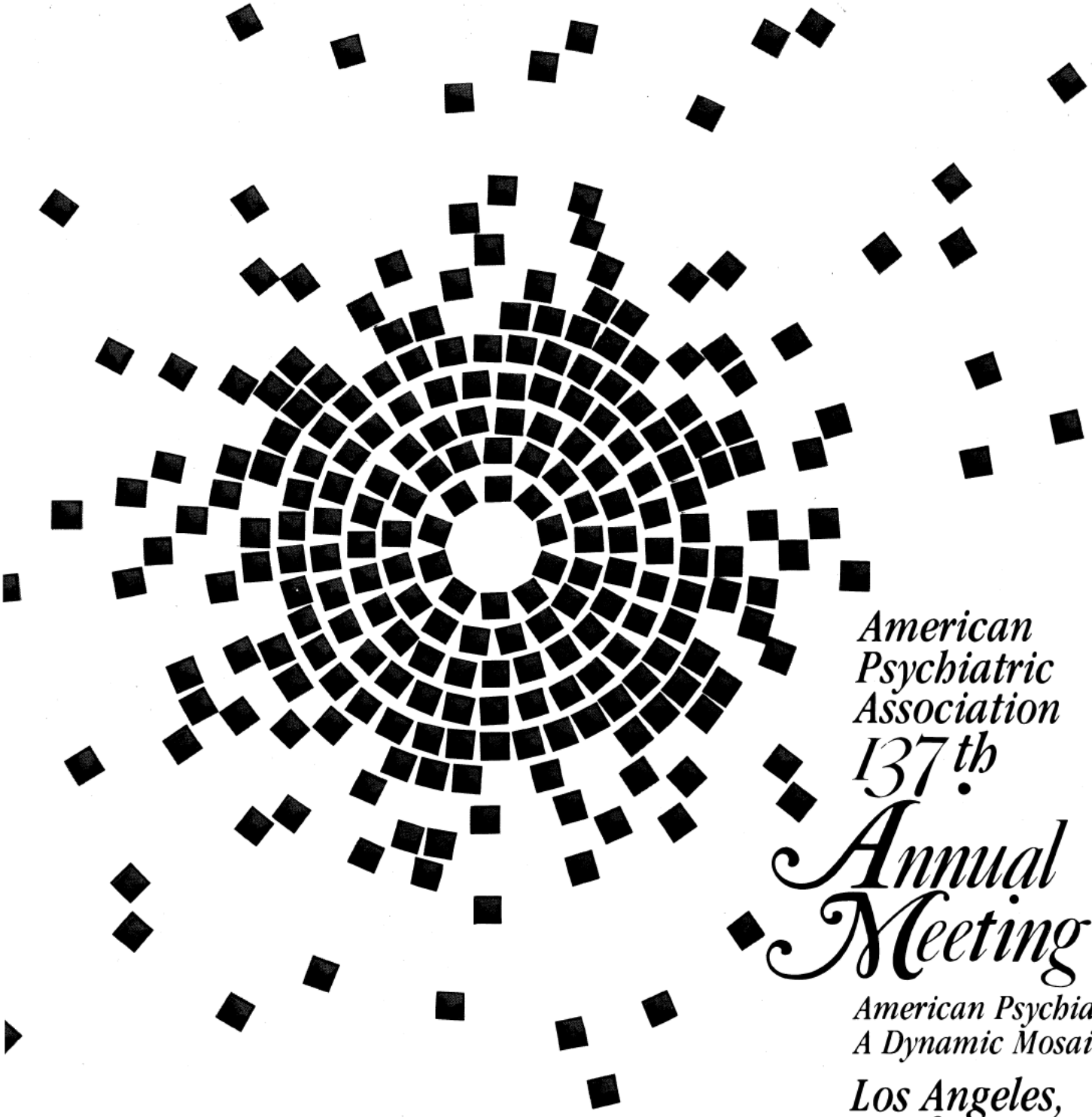

American Psychiatric Association

137th Annual Meeting

American Psychiatry: A Dynamic Mosaic

Los Angeles, California
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NEW RESEARCH ABSTRACTS

PAPERS ON NEW RESEARCH

IN SUMMARY FORM

THE ONE HUNDRED AND THIRTY-SEVENTH
ANNUAL MEETING OF THE
AMERICAN PSYCHIATRIC ASSOCIATION

LOS ANGELES, CALIFORNIA
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INDEX BY FIRST AUTHOR

Oral/Slide Papers

NR1 Monday, May 7, 2:00 P.M.

EEG SLEEP IN ELDERLY DEPRESSIVES AND DEMENTS

Charles F. Reynolds, III, M.D., Sleep Evaluation Center, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213, D.J. Kupfer, L.S. Taska, M.D. (1), C.C. Hoch, Ph.D. (1), D.E.. Sewitch, Ph.D. (1), B. Zimmer, M.D., R.S. Marin, M.D., J. Nelson, M.D., D.G. Spiker, M.D., D. Martin, M.D., R. Morycz, M.D., Pittsburgh, PA

Summary:

The physiology of sleep and its regulation in normal and pathologic aging continues to hold considerable clinical and theoretical interest. In the first phase of an NIMH-funded study (MH37869), we have compared the nocturnal EEG sleep patterns in three groups of subjects: healthy controls (n=25, age=69.0(5.0), M/F: 8/17); non-demented, non-delusional, major unipolar depressives (n=25, age=69.9(6.6), M/F: 4/21); and non-depressed probable Alzheimer's dementia patients (n=25, age=70.4(8.3), M/F: 7/18). Subjects had three consecutive nights of sleep studies after a two-week drug-free period. Scoring of NREM sleep was modified to quantify absence of stage-2 transients in some subjects, particularly the demented: thus, stage-2 was scored as stage "N" ("indeterminate") if an epoch (60 seconds) had a stage-2 appearance except for the absence of spindles, K-complexes, and V-waves. Selected EEG sleep variables were analyzed with one-way ANOVA (mean of nights 2 and 3):

	Controls	Depressed	Demented	F	p
Sleep Maintenance (%)	88.6 (7.3)	72.3 (14.1)	81.2 (10.4)	13.9	.0000
Stage "N" (%)	2.6 (6.2)	6.0 (12.9)	23.2 (27.9)	9.3	.0003
Stage REM (%)	20.2 (4.5)	24.9 (7.1)	17.8 (6.6)	8.6	.004
REM Latency (min)	57.6 (16.9)	33.3 (36.5)	52.1 (39.9)	3.8	.027
First REM Period (min)	19.3 (10.1)	25.8 (11.9)	14.3 (4.7)	9.5	.0002
First REMP Density	1.20(0.62)	1.66(0.77)	1.28(0.68)	3.2	.048

Examining REM latency distributions between depressives and dementing patients, we found that a cutoff score of 30 minutes (or less) correctly identified 70% of depressives and 80% of dementing patients, thus replicating our previously published retrospective finding (1). These data show differences in depressed and dementing patients in REM sleep (timing, amount, density, and temporal distribution), in NREM sleep (greater loss of stage-2 transients in dementing patients), and in degree of sleep fragmentation (greater in depressives).

1. Reynolds, C.F., et al: EEG sleep, aging, and psychopathology: New data and state of the art. Biol. Psychiat. 18(2):139-155, 1983.

NR2 Monday, May 7, 2:15 P.M.

EPIDEMIOLOGY OF AN AFFECTIVE DISORDERS CLINIC

Michael E. Thase, M.D., Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213, Jonathan M. Himmelhoch, M.D., Carilyn Z. Fuchs, Ph.D. (I), Pittsburgh, PA

Summary:

Epidemiologic methods have been fruitfully applied in many areas of medicine, and are increasingly used in psychiatric research. In this investigation, an epidemiological approach was applied to study the interrelationship of demographic variables, clinical factors, and diagnostic subtypes in a sample of 748 outpatients consecutively referred to a tertiary care Affective Disorders Clinic. All patients received a comprehensive neuropsychiatric evaluation, with clinical interviews complemented by medical assessments, detailed ascertainment of substance abuse patterns, and, in most cases, closely scrutinized electroencephalograms. Referral and final Research Diagnostic Criteria (RDC) diagnoses were grouped as: 1) bipolar disorder; 2) nonbipolar major depression; 3) depression secondary to nonaffective psychiatric disorders; 4) depression secondary to medical or neurological disorders; and, 5) schizoaffective disorder. The most striking finding was the discrepancy between referral and final diagnoses of nonbipolar major depression: only 50% (140 of 279) of such patients met RDC for diagnosis of unipolar major depression after comprehensive assessment. These patients frequently had unrecognized, nonaffective primary psychiatric syndromes (n=68), primary substance abuse disorders (n=32), or medical-neurological conditions (n=30). In contrast, referral diagnosis of bipolar disorder was correct in 86% of cases ($p < .001$). Misdiagnosis of unipolar depression was significantly more likely in patients with substance abuse ($p < .001$), in men ($p < .01$), and in younger patients ($p < .001$). Several demographic variables discriminated between subtypes of affective disorder. Nonbipolar syndromes showed a significant preponderance of females; bipolar disorder was nearly equally common in men and women ($p < .01$). Patients with schizoaffective disorder or depression secondary to nonaffective RDC disorders were significantly younger ($p < .001$), less likely to be married ($p < .001$), and of lower socioeconomic status ($p < .05$). Global ratings of illness severity were highest in schizoaffective and bipolar subtypes, while self ratings of depression were highest in RDC secondary depressives. Substance abuse was rampant (54% of all referrals), and was significantly higher in men ($p < .001$) and nonbipolar depressives ($p < .001$). Results provide further evidence of the heterogeneity of nonbipolar major depression. In particular, prevalence of nonbipolar depression is reduced markedly when secondary depressive syndromes are carefully ascertained and separately considered. Further, epidemiological differences between subtypes of affective disorder provide some validation of their independence.

NR3 Monday, May 7, 2:30 P.M.

BETA AND SEROTONIN RECEPTOR FUNCTION IN DEPRESSION

J. John Mann, M.D., Payne Whitney Clinic, 525 East 68th Street, New York, NY 10021, Richard P. Brown, M.D., James H. Halper, M.D. (I), John Sweeney, Ph.D. (I), P. Anne McBride, M.D., John P. Bilizekian,M.D. (I), Marc E. Weksler, M.D. (I), Peter E. Stokes, M.D., New York, NY

Summary:

Background: Somatic antidepressant treatment is characterized by delayed effects upon beta and/or serotonin$_2$ (5-HT$_2$) receptor sensitivity or number in animal studies. It has been postulated that these receptor effects mediate the antidepressant effect. Such findings raise the question of whether beta or 5-HT$_2$ receptor measures are altered in depressive disorders? Methods: Since, central beta receptors and 5-HT$_2$ binding sites are inaccessible we have developed a method for measuring beta receptor binding indices (Bmax and K_D) and isoproterenol-generated cAMP response in parallel on split samples of intact lymphocytes that requires only a small quantity of blood and is therefore, suitable for clinical studies. We have also characterized a 5-HT$_2$ binding site on intact platelets. We measured lymphocyte beta receptor binding indices and isoproterenol-generated cAMP response and platelet 5-HT$_2$ binding in a series of drug-free inpatients with melancholia and in healthy controls. Results: Significantly lower isoproterenol-generated lymphocyte cAMP response was found in depressed patients compared to controls. No differences were seen in beta receptor binding indices. Patients with agitated depression showed significantly lower cAMP response to isoproterenol than patients with retarded depression. Preliminary platelet 5-HT$_2$ binding data and the relationship of these receptor changes to hypothalamic-pituitary-adrenocortical function in this patient population will also be presented. Conclusions: Our finding of a downregulation of lymphocyte cAMP response to isoproterenol in the absence of any alteration in beta receptor binding indices suggests that there is a relative uncoupling of beta receptors binding sites in melancholia from adenylate cyclase or that the downregulation of the cAMP response has occurred distal to the binding site. There appeared to be a subgroup of agitated depressives with markedly downregulated beta receptors and a subgroup of depressed patients with normal beta receptor function. No subgroup was found with supersensitive beta receptors. Such data are consistant with studies reporting elevated or normal, but not low, peripheral adrenergic function in depressive disorders. The relationship of these clinical and biochemical subgroups of depression to 5-HT$_2$ binding measures and hypothalamic-pituitary-adrenal function will be discussed.

NR4 Monday, May 7, 2:45 P.M.

CLINICAL UTILITY OF DST IN PREPUBERTAL CHILDREN

Elizabeth B. Weller, University of Kansas Medical Center, 39th and Rainbow, Kansas City, KS 66103, M.D., Ronald A. Weller, M.D., Mary A. Fristad, M.A. (I), Marijo Teare, B.S. (I), Kansas City, KS

Summary:

The dexamethasone suppression test has been used as a biological marker of depression in adults. Approximately 40-60% of adults with endogenous depression fail to suppress cortisol secretion when given dexamethasone. Recently many reports have appeared concerning the usefulness of DST in evaluating adults. However, few studies have examined the DST in depressed prepubertal children. Early studies indicate sensitivity of 14-79% and specificity of 89% of the DST in children. However, the number of subjects in these studies have been small.

To date there have been no studies comparing results of the DST in depressed children, psychiatric controls, and normal controls. Also there have been no reports of baseline cortisol levels in these groups, or of changes in the DST with treatment. This study was designed to address these issues. Subjects were aged 6-12 years. The DSM-III depressed group (N=34) and psychiatric control group (N=17) were inpatients; the normal control group (N=18) were from the community. Baseline cortisol levels were obtained at 8 a.m. and 4 p.m. Then subjects were given .5 mg dexamethasone at 11 p.m. and cortisol levels were measured at 8 a.m. and 4 p.m. the next day.

Depressed patients had higher mean baseline cortisol levels at both 8 a.m. and 4 p.m. than did psychiatric or normal controls. The difference between the depressed and normal control groups were statistically significant at 4 p.m. ($p < .001$). Following dexamethasone administration 79% of depressed children failed to suppress cortisol secretion compared to 29% of psychiatric controls and 11% of normal controls. Fourteen of the depressed children were reassessed with the DST and clinical global impression (CGI) ratings several times over a 4-8 period. Results indicated that continued failure to suppress cortisol secretion is correlated with poor clinical outcome.

This study shows that baseline cortisol levels in depressed children are elevated in comparison with non-depressed children and that failure to suppress cortisol on the DST is associated with depression in children. Followup DSTs lend information concerning clinical outcome. In summary, it appears that DST has definite clinical application in assessing depression in prepubertal children.

NR5 Monday, May 7, 3:00 P.M.

SUICIDE AND FAMILY LOADING FOR AFFECTIVE DISORDERS

Janice A. Egeland, Ph.D. (I), University of Miami, Amish Study, North Research Division, 49 Sylvania Road, Hershey, PA 17033; James N. Sussex, M.D., Miami, FL

Summary:

What is peculiar about suicide in a pacifistic, religious group that has a 300 year history of non-violence (no murders, criminal records) does not engage in alcohol or drug abuse, enjoys high social cohesion, has no divorce or family dissolution and where the ultimate sinful act is the taking of any life, including one's own? The peculiar fact is that one finds any suicides in such a setting.

Research Setting: This is the first report of suicide data from the Amish Study. All suicides from a 100 year period (1880-1980) were ascertained in this genetic isolate in southeastern Pennsylvania. There were 26 suicides composed of 21 males and 5 females. These suicides showed a definite pattern over time. They were all done by lethal means (2 drownings, 4 gun shots, 20 hangings) not by uncertain gestures (gas or pills). There were definite seasonal and calendric patterns: a. two peaks corresponding to March-May and September-November; b. a primary peak on Monday followed by Wednesday-Thursday (but NEVER on Sunday); and c. a clear peak early each month with the greatest number on the 5th, a finding recently reported for the first time (MacMahon, Am.J.Epidemiol. 117:744-50, 1983). The biological, as well as sociological, implications will be reviewed.

Diagnostic Data: A five member Psychiatric Board diagnosed the cases according to the RDC. Twenty-four met criteria for a major affective disorder: UP=10, UP tagged for BP=2, BP II=4 and BP I=8. One case was minor depression and one was "unspecified psychiatric".

Family Histories: All the BP suicides had first or second degree relatives with BP/UP disorders and heavy family loadings. The same was true for the "unspecified psychiatric" suicide and all except four UP's. These four had heavy family loadings for unipolar depressive, anxiety and personality disorders. There was a total absence of any mental illness in the extended family for the single suicide diagnosed as a minor depression. Morbid risks are being calculated for suicide pedigrees and a sample of control AD pedigrees.

Suicide Pedigrees: A dramatic result was the extent to which the 26 suicides clustered in a few multigenerational pedigrees among the multiple ones ascertained with affective disorders. These pedigrees will be shown. A possible genetic factor in the transmission of both affective disorders and suicide will be discussed. The clinical significance relates to the need for psychiatrists to obtain complete family histories as part of the assessment of suicidal risk for any patient with a major affective disorder.

NR6 Monday, May 7, 3:15 P.M.

IMIPRAMINE FOR TREATMENT OF CHRONIC DEPRESSION

James H. Kocsis, M.D.,Payne Whitney Clinic, 525 East 68th Street, New York, NY 10021, Allen J. Frances, M.D., J. John Mann, M.D., New York, John Sweeney, Ph.D. (1), White Plains, NY; Carlyle Voss, Portland, ME

Summary:

Chronic depression is common among psychiatric outpatients and has traditionally been considered resistant to either drugs or psychotherapy. However, recent open studies have suggested that antidepressant medication may be useful in a substantial portion of this population. We will report preliminary results of a prospective, double-blind, placebo-controlled trial of Imipramine (IMI) for treatment of chronic depression.

Methods: 36 outpatients who fulfilled DSM III criteria for either Major Depression or Dysthymic Disorder, and who complained of depressed mood and associated dysthymic symptoms for longer than two years were studied. 24 of these did not improve during a two-week single blind placebo period and agreed to participate in a six-week double-blind comparison of IMI and placebo. Patients were rated at weeks -2, 0, 4 + 6 using the 24 item HAM-D, GAS and a dysthymic symptom checklist. At baseline most subjects showed "double-depression," i.e., Major Depression superimposed on Dysthymic Disorder. At termination patients were classified as (a) recovered from superimposed Major Depression only (b) recovered from both Major Depression and Dysthymic Disorder or (c) not recovered. Recovered patients receiving IMI were continued on drug and reexamined at six months.

Results: 6/10 (60%) of IMI-treated and 1/13 (8%) of placebo-treated patients were found recovered from both superimposed Major Depression and dysthymic symptoms at the end of the six-week double-blind period (p .025 by FET). Two additional placebo-treated patients showed partial recovery, i.e., from superimposed Major Depression only. The remaining 40% of IMI and 77% of placebo subjects were not recovered. 4/4 IMI responders were still completely recovered at six-month follow up. Favorable IMI response was significantly associated with positive family history of depression. Current presence of DSM III melancholia was associated with poor placebo response.

Significance: This is the first double-blind, placebo-controlled study to prospectively examine efficacy of antidepressant medication in a sample of patients with chronic depression. Preliminary results indicate the IMI produced significantly more complete recovery than placebo in patients with "double depression," and that such response is enduring.

NR7 Monday, May 7, 3:30 P.M.

DESIPRAMINE LEVELS AND RESPONSE IN ELDERLY MELANCHOLICS

J. Craig Nelson, M.D. (I), 20 York Street, New Haven, CT 06504, Peter I. Jatlow, M.D. (I), Carolyn Mazure, Ph.D. (I), New Haven, CT

Summary:

It is frequently suggested that elderly depressed patients should be treated with lower doses of tricyclic antidepressants. It is well established that the elderly are at greater risk for side effects[1]. It would be reasonable to suspect that elderly patients might be more sensitive to the antidepressant effects of tricyclics and that they would respond at lower plasma concentrations of these drugs. However, there is little data to address this clinically important question. As part of an ongoing study of desipramine (DMI), we have examined the relationship of response and plasma DMI concentration in depressed patients over 60 and present our findings here.

During a 5 year period 70 depressed patients over the age of 60 were treated with DMI. Only 25 met DSM III criteria for major depression with melancholia, were unipolar, were not delusional, were without active medical illness or definite brain disease, and were still depressed after one week of hospitalization off psychotropic drugs. DMI was given for 3 weeks at 2.5 mg/kg. Symptoms were rated on a 24-item Hamilton rating scale. Response was defined as a post-treatment Hamilton score of 11 or less. The steady state DMI level was an average of 2 or more samples from the second and third week of treatment.

Four patients with major adverse reactions and three with emergence of psychotic symptoms failed to complete the drug trial. Of the 18 completers, 14 were female. Their mean age was 70 (range 60-82). Fifteen had stable medical illness. Their mean pretreatment Hamilton score was 29. DMI steady state levels ranged from 16 to 502 ng/ml (median=102).

Six patients responded to the 3-week fixed dose trial; 12 did not. DMI levels of responders (median=126) were higher than those of nonresponders (median=81, Mann-Whitney test, $p<.05$). The plasma level which maximally and significantly separated responders and nonresponders was 115 ng/ml; above this level 4 of 5 responded, below it 2 of 13 responded (Fisher exact test, $p<.025$). Five patients not responding to the initial 3-week trial responded when DMI was increased and the plasma level rose to above 115 ng/ml. Among all patients treated with DMI to a plasma level above 115 ng/ml, 64% (9 of 14) responded.

The data indicate that elderly melancholic patients do not respond to lower DMI plasma concentrations and that levels similar to those reported for melancholic patients of all ages[2] are required. Doses similar to those of younger patients were needed to reach these levels.

1 Nelson JC, et al. Arch Gen Psychiatry 39:1055-1061, 1982.
2 Nelson JC, et al. Arch Gen Psychiatry 39:1419-1422, 1982.

NR8 Monday, May 7, 3:45 P.M.

MEMORY DEFICITS WITH ECT: PERSISTENT EFFECTS

Richard D. Weiner, M.D., Psychiatry Service, Durham VA Medical Center, Durham, NC 27705, Helen J. Rogers, Ph.D. (1), Jonathan R.T. Davidson, M.D., Larry R. Squire, Ph.D. (1), Durham, NC 27705

Summary:

Whether treatment-associated memory deficits are transient or long lasting has been a prime area of concern with respect to ECT use. The vast majority of studies considering objective measures of memory function have reported that ECT-associated changes disappear over a period of days to weeks. Still, investigations which have focused upon personal or autobiographic memory, along with some of those which have considered subjective or self-rated memory, have continued to provide suggestive evidence for at least occasional persistent spotty losses. Much of this work, however, has not controlled for the effects of the underlying psychiatric disorder upon memory function, making the specific contribution of the ECT, itself, unclear. As part of a larger study, 36 depressed patients (per Feighner criteria) referred for ECT were randomly assigned to either unilateral nondominant (d'Elia type) or bilateral electrode placement and to either brief pulse or sine wave stimuli, and completed testing with a variety of measures of memory function at all three of the following: upon study entry, 2-3 days following completion of the ECT course, and six months later. Fourteen clinically matched subjects who were not referred for ECT, and were tested at analogous times, served as controls. Memory measures included recall of newly learned verbal and figural information, recall of remote (pre-ECT) impersonal and autobiographic material, and subjective ratings of memory function. A number of prominent acute amnestic changes were observed, with bilateral electrode placement and sine wave stimuli consistently being associated with a greater degree of deficit, both with respect to baseline measures and in comparison to responses of control subjects. As expected, no evidence of anterograde or remote impersonal memory impairment was present by six months post-ECT. Personal memory function, however, continued to show evidence of residual deficits, but only for subjects receiving bilateral electrode placement ($BL > C$, $p < 0.001$; $BL > UL$, $p < 0.003$). This finding appears to be independent of stimulus waveform, and, interestingly, was uncorrelated with overall subjective ratings of memory function. The significance of these findings will be discussed, with particular attention to the unique advantages and disadvantages of autobiographic memory assessment and their effects upon the interpretation of data collected using such a measure.

NR9 Monday, May 7, 4:00 P.M.

EFFECTS OF ECT GIVEN TWO VERSUS THREE TIMES WEEKLY

David A. McAllister, Ph.D. (I), Psychology Service (116B), VA Medical Center, Indianapolis, IN 46202, Albert Sattin, M.D., Michael G. Perri, Ph.D. (I), Frederick P. Rauscher, M.D., Randall C. Jordan, M.D., Indianapolis, IN

Summary:

Electroconvulsive therapy (ECT) has consistently been shown to be effective for treating depression despite variations in the frequency and total number of treatments. Some animal research (Chiodo & Antelman, 1980) has also shown that a single ECT treatment may have biochemical effects equal to those of multiple treatments. These previous findings suggest that the benefits of ECT may be largely independent of treatment frequency. The side-effects, though, are probably closely related to frequency and total number of sessions. Most notably, disruption of the ability to form new memories has been reported to become worse with increasing numbers of treatments. The present study has begun a test of these hypotheses by comparing the effects and side-effects of ECT given two versus three times per week.

Subjects were depressed inpatients assigned randomly to receive ECT two (n = 8) or three (n = 10) times weekly. Depressive symptoms, general psychiatric status, memory and visual-spatial problem solving were tested by one of two blind examiners at pretreatment and after two and four weeks of ECT. The preliminary analyses reported here used 2x2 repeated measures analyses of covariance (Time X Condition) on change scores, with pretreatment scores as covariates. Results indicate that depression improved over Time on self-report measures (Beck Depression Inventory; $p < .02$) and on observer ratings (Hamilton Rating Scale; $p < .004$). There were no other significant effects on these measures. A similar pattern of improvement over Time was seen in general psychiatric status (Brief Psychiatric Rating Scale; $p < .005$) and verbal memory (Wechsler Memory Scale, Logical; $p < .008$), with no Condition or Interaction effects. Measures of visual-spatial abilities, though, produced a different pattern. The twice-per-week group improved more than the other group on visual scales from the Wechsler Memory Scale ($p < .0003$) and on the Porteus Mazes ($p < .06$). These visual-spatial measures had no Time or Interaction effects.

These results suggest ECT is equally effective at reducing depressive symptoms and improving psychiatric status whether given two or three times per week. This lifting of depression apparently also produces improvements in verbal memory that are equal in the two conditions. In visual-spatial skills, however, the twice-weekly group consistently performed better than the other group. This suggests that ECT given three times per week has some disruptive effects on higher cortical functioning that are avoided with only two sessions weekly. This effect is presumably seen only in visual-spatial skills due to the use of right unilateral ECT.

NR10 Monday, May 7, 4:15 P.M.

DEPRESSED CHILDREN: DESIPRAMINE NOT IMIPRAMINE MEDIATES RESPONSE

Sheldon H. Preskorn, M.D., Kansas University Medical Center, 39th and Rainbow, Kansas City, KS 66103, Elizabeth B. Weller, M.D.,Ronald A. Weller, M.D., Carroll W. Hughes, Ph.D. (1), Kelly N. Bolte (1), Kansas City, KS

Summary:

Major depressive disorders occur in children. Response to imipramine varies substantially when plasma drug monitoring is not performed. This study was designed to determine the relationship between plasma levels of imipramine (IMI) and its metabolites [desipramine (DMI), 2OH-DMI and 2OH-IMI], and clincal response in depressed children. Subjects were 32 children 6-12 years of age who satisfied DSM-III criteria for major depression of at least 30 days duration. All of the subjects required hospitalization and had received no prior treatment with tricyclic antidepressants. Children with seizures, cardiac disorders or schizophrenia were excluded.

There were 3 study phases: I) 2 weeks of drug free in-hospital observation and psychotherapy; II) 75 mg of imipramine administered qhs for 3 weeks; and III) 3 additional weeks at an altered dose for those patients who did not respond on the 75 mg dose. Severity of depression was measured using the Childhood Depression Inventory (CDI), Childhood Depression Rating Scale (CDRS), and a global rating at admission and after each phase. Plasma samples were obtained at day 10, 14 and 21 of Phases 2 and 3. The assay separately quantitated IMI, DMI, 2OH-IMI, and 2OH-DMI. The study was double blind with regard to plasma drug concentration.

No improvement occurred in phase I. In phase II, response was evaluated by the residuals of the CDI and CDRS based on the two drug free scores. Response was plotted as a function of plasma drug level. As assessed by the CDI, response was linearly related to parent drug (IMI) levels ($R^2 = 0.15$, $p < .03$). A curvilinear rather than a linear relationship existed between response and both DMI levels alone ($R^2 = 0.38$, $p < .002$) and the total of IMI plus DMI. The latter analysis accounted for 55% of response variability. Levels of the hydroxymetabolites did not appreciably add to response prediction. Standarized regression coefficients suggest that DMI is 2.5 times more potent that IMI as an antidepressant in children. Similar results were obtained with the CDRS response data. Using the previously developed range (1) of 125-225 ng/ml for IMI + DMI, response rates within versus outside of this range were 73% vs 20% for Phase II respectively. If the range is expanded to 115-250 ng/ml, the results are 73% vs 6%. Phase III results supported the conclusions derived from Phase II.

(1) J Clin Psychiatry 43:450-453,1982. Supported by Research Scientist Development Award MH-00272 (SHP) and NIMH grant MH 36373.

NR11 Monday, May 7, 4:30 P.M.

AFFECTIVE DISORDERS IN RELATIVES OF BORDERLINES

Patricia M. Schulz, M.S.W. (I), Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213, S. Charles Schulz, M.D., Solomon Goldberg, Ph.D. (I), Robert Hamer, Ph.D. (I), Prakash G. Ettigi, M.D., Pittsburgh, PA; Robert O. Friedel, M.D., Richmond, VA

Summary:

Introduction: The family aggregation of schizophrenia and affective disorders has been well established, and furthermore a genetic predisposition is inferred from studies separating genes and environment. The epidemiological studies are important first steps in understanding purported genetic predispositions to mental illness as well as definition of "spectrum" disorders. Family aggregation studies have been performed in borderline personality disorder, but none of the investigators interviewed the relatives directly. The purpose of this study was to directly interview the first degree relatives of patients identified as borderline personality disorder (BPD), schizotypal (ST), or both (BPD/ST). Methods: Forty-four first degree relatives of 22 study patients were interviewed using the Diagnostic Interview Schedule (DIS) administered by a trained interviewer (PMS). The DIS is a structured interview which leads to DSM-III Axis I diagnoses. Study patients (N=30) were also assessed using the DIS. Results were compared to normal population results of DIS administration at 3 major centers (N=12,000 approx.) Results: 1) Relatives of BPD/ST patients had higher rates of affective disorder (52%) than both the depression (34.8%) and DIS normative (5.8%) populations. 2) No cases of schizophrenia were identified in the first degree relatives of either patient group. 3) Alcoholism was found in 16% of BPD/ST patient's relatives, a rate comparable to the relatives of depressed patients (21.2%) and normative group (14.3%). 4) Antisocial personality disorder was seen more frequently in the relatives of the depressed group (13.6%) than in the BPD/ST (2.2%) or normative group (2.7%). Discussion: The rate of depression in the first degree relatives of BPD/ST patients bolsters the argument of some investigators that BPD borders or is a variant of affective disorder. The lower rates of schizophrenia, alcoholism and antisocial personality disorder are counter to common expectation and speak against the contention that BPD/ST relatives have a higher rate of all disorders. The association between the two diagnoses suggests the possibility that patients with the combined diagnoses may be treatable with antidepressant medication.

NR12 Monday, May 7, 4:45 P.M.

A DOUBLE-BLIND STUDY OF PHENELZINE IN BULIMIA

B. Timothy Walsh, M.D., New York State Psychiatric Institute, 722 West 168th Street, New York, NY 10032, J.W. Stewart, M.D., S.P. Roose, M.D., J.S. Carino, M.D., M. Gladis (I), A.H. Glassman, M.D., New York, NY

Summary:

The presence of prominent depression and anxiety among patients with bulimia and the encouraging results of open treatment of such patients with monoamine oxidase inhibitors prompted us to initiate a double-blind, placebo-controlled trial of phenelzine in bulimia. We here report the preliminary results of that trial which show that phenelzine has an impressive therapeutic effect.

Patients were selected to be normal weight females between the ages of 18 and 45 who met DSM-III criteria for bulimia, had been ill for over one year and binged at least 3X/week. Patients were initially treated with placebo in single-blind fashion for 2 weeks. Patients who continued to binge at least 3X/week were then randomly assigned to either phenelzine (60 to 90 mg/day) or placebo and treated for an additional 8 weeks. Twenty patients have been randomized and have completed the protocol. Nine were treated with phenelzine and 11 with placebo. At randomization, the phenelzine and placebo treated groups did not differ in number of binges per week (10.8 vs. 11.1, $p > 0.9$), score on the Eating Attitudes Test (EAT) (36.0 vs. 42.5, $p > 0.2$), or score on the 17-item Hamilton Depression Scale (HDS) (10.0 vs. 8.7, $p > 0.4$). At completion, however, the phenelzine-treated group reported significantly fewer binges per week (2.6 vs. 10.5, $p < .01$) and had a lower EAT score (24.1 vs. 45.5, $p < .01$). Five of the 9 phenelzine-treated patients ceased binging entirely and the other 4 reduced their binge frequency by at least 50%; none of the 11 placebo-treated patients stopped binging and only 2 reduced their binge frequency by 50% or more. Probably because most patients were not severely depressed and because some side effects of phenelzine are rated on the HDS, the phenelzine- and placebo-treated groups did not differ on this measure at completion (6.5 vs. 9.7, $p > 0.2$). No patient experienced a hypertensive reaction during the study.

These data demonstrate that phenelzine is substantially more effective than placebo in the treatment of patients with bulimia and suggest that there may be an important place for this medication in the therapy of this eating disorder.

Oral/Slide Papers

NR13 Tuesday, May 8, 10:15 A.M.

DEPRESSION AND ANXIETY AMONG MEDICAL STUDENTS

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Summary:

A longitudinal study in progress provides the opportunity to track psychiatric vulnerability among medical students. Although it has been suggested in the literature that depression and anxiety are common types of disturbance, little is known about how the prevalence rate of depression or anxiety changes over the course of medical school and what factors influence the changes. This paper will examine psychiatric distress in medical students at two points in time. At orientation, 138 medical students from one school (95% of the class) and 123 medical students from another school (69% of the class) responded to a survey by questionnaire. The information gathered included ratings of depression and anxiety (using the Zung Self-Rating Depression Scale and Self-Rating Anxiety Scale) At the end of their pre-clinical training (second year) the two classes were re-surveyed.

At the time they entered medical school, the students' mean depression score was 41 and the mean anxiety score was 39. The depression mean was not only higher than the control group of normals ($\overline{X}$ = 33; Zung, 1965) but 13% of the students fell into the range of scores commonly found among depressed patients (scores of 50 or more). In contrast, the anxiety mean was also higher than the control group's ($\overline{X}$ = 33.8; Zung, 1971) but only 1% of the students fell into the range characteristic of patients with anxiety disorders (scores of 58 or more). There were no differences between schools in either depression or anxiety. There were no sex differences in depression, but women students reported significantly higher anxiety than the men ($\overline{X}$ = 41.3 compared to $\overline{X}$ = 37.9, $p < .001$).

At the end of their pre-clinical years the means of both depression and anxiety scores were virtually identical to those at orientation. However, the proportion of students with depression scores as high as those found among depressed patients had risen to 24.5%; 2.5% of the students had anxiety scores in the range commonly found among patients with anxiety disorders. Further, although there were still no differences between schools on either anxiety or depression, women students were significantly more anxious ($p < .05$) and more depressed ($p < .05$) than men. Among the women 31.5% fell into the clinically depressed range while 16.2% of the men did. All of the students who fell into the clincally anxious range were women (7.4% of the women).

These results suggest that there may be a particular group of medical students who are at risk for developing psychological distress during the medical training period. Potential etiologic factors and implications of these findings will be discussed.

NR14 Tuesday, May 8, 10:30 A.M.

MAJOR DEPRESSION IN AGORAPHOBIA-PANIC PATIENTS

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Summary:

The longitudinal relationship of Major Depression (MD) and Agoraphobia-Panic Disorder (AGR-PD) is not known. This study examined that relationship in 60 patients with AGR-PD. Methods: Sixty consecutively admitted patients to an anxiety disorders clinic who met Research Diagnostic Criteria (RDC) for Agoraphobia, Mixed Phobia, or Panic Disorder, comprised the sample. Data was collected through direct interviews using 1) the Schedule for Affective Disorders and Schizophrenia (SADS-L), 2) a modified anxiety section for the SADS-L developed by Fayer and Endicott, and 3) a semistructured interview developed by the authors that reviewed the history of depressive symptoms and anxiety symptoms in a year-by-year manner. RDC was used to diagnose all episodes of MD.
Results: Of 60 patients, 41 (68%) had a post and/or current episode of MD. Twenty patients had a primary episode of MD that occurred prior to the onset of panic attacks. Seventy-five percent of these 20 patients had a primary MD episode that was temporally separate from panic attacks with an average of 3 years separating the end of the primary depressive episode and the first panic attack. Of the 41 patients with a history of MD, 35 had at least one episode of endogenous type MD.

Patients with a history of MD had more panic attacks ($p<.005$), higher phobic scores (Wolpe-Lang Fear Survey, $p<.005$), higher clinician rated anxiety (Hamilton Anxiety Scale, ($p<.001$) and depression (Hamilton Depression Scale, $p<.001$) as well as higher scores on the Patient Rated Anxiety Scale ($p<.001$) compared to patients without MD. The patients with a history of MD also had a greater duration of Panic Disorder ($p<.05$) and higher ratings of worst past level of impairment secondary to panic attacks ($p<.01$) and agoraphobia ($p<.001$). Similar findings were obtained when patients with current MD (N=11) were excluded from the analysis. There were no significant differences between patients with primary MD and those with secondary MD on any of the above severity measures.

It is concluded that MD commonly occurs in patients with AGR-PD, that it occurs at times temporally separate from AGR-PD, and the AGR-PD symptoms of patients with a history of MD appears to be more severe. The high rate of occurrence of both MD and AGR-PD in patients may be attributable to a common genetic loading for these disorders. It is possible that a common neurobiological substrate may exist for some forms of anxiety and depression.

NR15 Tuesday, May 8, 10:45 A.M.

A FAMILY STUDY OF PANIC DISORDER AND AGORAPHOBIA

Russell Noyes, Jr., M.D., University of Iowa, Department of Psychiatry, Iowa City, IA 52242, Raymond R. Crowe, M.D., Iowa City, IA; Emily Harris (I), Pittsburgh, PA; Badri Hamra (I), Cheryl McChesney (I), Iowa City, IA

Summary:

A family interview study of panic disorder and agoraphobia was undertaken for the purpose of comparing the familial distribution of these disorders.

Forty probands that met DSM-III criteria for panic disorder were age- and sex-matched with 40 that met criteria for agoraphobia. They were selected from patients attending a psychiatric clinic and an agoraphobia self-help group. Twenty age- and sex-matched control probands without anxiety disorders were selected from hospital employees. All available first-degree relatives were personally interviewed by a research assistant according to a structure format. Information on relatives that refused to be interviewed or were deceased was obtained from the remaining relatives. Diagnoses were made according to DSM-III criteria and were made blindly by two psychiatrists reviewing interview data. Diagnoses on relatives not available for interview were made according to criteria for family history diagnoses established by Andreasen et al.

The prevalence of panic disorder was found to be increased among the relatives of both panic disorder and agoraphobic probands (7.0% agoraphobic, 15.1% panic disorder and 3.5% control); the prevalence of agoraphobia was increased among the relatives of agoraphobic probands (9.4% agoraphobic, 1.7% panic disorder and 3.5% control). The frequency of primary affective disorders was not increased in either group of relatives (4.7% agoraphobic, 4.2% panic disorder and 7.1% control) but alcohol disorders were more frequent among the male relatives of agoraphobic probands (12.9% agoraphobic, 6.7% panic disorder and 4.4% control). Probands and relatives with agoraphobia were found to have an illness characterized by an earlier onset, more severe symptoms, more frequent complications, and less favorable outcome than probands and relatives with panic disorder. Relatives of probands with secondary depression had a higher risk for anxiety and alcohol disorders than did relatives of probands without secondary depression. However, the risk for affective disorders was no different.

This study confirms that panic disorder and agoraphobia are familial. It suggests that agoraphobia is a more severe variant of panic disorder but demonstrates no relationship between anxiety disorders and primary affective disorders.

NR16 Tuesday, May 8, 11:00 A.M.

THE CARDIOVASCULAR SYSTEM IN PANIC DISORDER

M. Katherine Shear, M.D., Payne Whitney Clinic, 525 East 68th Street, New York, NY 10021, H. Jonathan Polan, M.D., Greg Harshfield, Ph.D. (I), Richard Devereus, M.D. (I), Allen J. Frances, M.D., J. John Mann, M.D., Thomas Pickering, M.D. (I), Randi Kramer-Fox (I), New York, NY

Summary:

Background: The finding of a high incideuce of mitral valve prolapse in panic patients, coupled with the sudden unpredictable appearance of cardiovascular symptoms during panic episodes, has led to speculations that primary cardiovascular dyfunction is important in the etiology of panic disorder. We tested this hypothesis in 3 studies: 1)Laboratory testing of cardiovascular reflex responses 2)Echocardiographic study for MVP. 3)24 hour ambulatory BP monitoring during a normal working day. Methods: 1)19 drug free patients with DSM III diagnoses of panic disorder or agoraphobia were compared to 17 normal controls by measuring HR and BP responses to deep breathing, standing for 3 minutes, return to recumbency and valsalva maneuver. 2)25 patients with the same DSM III diagnoses underwent echocardiographic study and were compared to 200 normal controls. 3)A different group of 19 panic or agoraphobic patients wore ambulatory BP monitors for a 24 hr period and were compared to 30 normal controls. Results: 1)The reflex study showed little difference from controls. Patients had significantly less mean HR increase from baseline at 30,60,90, seconds after standing and significantly greater means HR decreases at 90 seconds after return to recumbency. However, mean HR levels of patients were not significantly different from controls HR at these times. 2)Only 2 of the 25 patients had echocardiographic evidence of MVP. This was not different from the 3% incidence in the control population. 3)In the 24 hr monitoring study, mean BP's in different activities of the anxiety disorder group were not different from controls: (work:pt 122/77 control 120/83 home: pt 111/74 control 114/74; misc:pt 112/80 control 121/82; Sleep: pt 101/67 control 102/67). 9 pts had monitored partial (4)or full blown (5)panic attack. Mean BP for full blown (122/90) and partial (115/81) attacks were significantly higher than mean BP during non anxious periods (107/90 but were not higher than mean BP during mild physical activity (122/90) Significance: These studies show clear evidence of normal or low normal but not increased cardiovascular reactivity in panic patients during laboratory reflex testing and in normal daily activities. The incidence of MVP was no higher than a control group. The findings suggest that primary cardiovascular dysfunction is not an important factor in the etiology of panic attacks, and instead, indirectly implicate the etiologic importance of central nervous system dysfunction.

NR17 Tuesday, May 8, 11:15 A.M.

BENZODIAZEPINE RECEPTOR SENSITIVITY IN HUMANS

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Summary:

Benzodiazepines are the most commonly prescribed of all psychotropic drugs. Specific receptors for benzodiazepines have been identified in brains of many species, including man. Since the sensitivity of these receptors may be abnormal in neuropsychiatric disease, we initiated a series of studies designed to measure benzodiazepine receptor sensitivity in humans. Intravenous administration of diazepam to 10 normal volunteers was carried out and the effects of increasing doses of diazepam on the velocity of saccadic eye movements, memory performance and plasma catecholamines were measured and used to construct diazepam dose-response effect curves for each of these variables. These dose effect curves provide a measure of benzodiazepine receptor sensitivity in a normal human population. Diazepam or saline placebo were administered in a single-blind fashion. The doses of diazepam were 4.5 µg/kg, 4.5 µg/kg, 9 µg/kg, 18 µg/kg, 36 µg/kg and 72 µg/kg. Infusions were separated by 15 minute intervals during which saccadic eye velocity was measured using infrared oculography and blood was drawn for catechloamines. After the second, fourth and sixth infusion a test of verbal memory and attention was given.

Diazepam produced a significant dose dependent decrease in the velocity of large amplitude saccades. Diazepam also decreased plasma epinephrine and norepinephrine in a dose-dependent manner. Similarly diazepam produced a specific dose-dependent impairment in recent memory in the absence of any effects on attention or access to semantic memory. Diazepam produced an increase in the number of intrusion errors in the free recall of recently learned information as well as increasing the number of false identifications in a recognition task of recently learned information. Preliminary analysis of this data indicates that the slopes of the diazepam dose effect curves for saccadic velocity, plasma norepinephrine and memory performance are similar. This suggests that these effects may be mediated by a specific benzodiazepine receptor and provide a quantitative approach to the measurement of human benzodiazepine receptor sensitivity. Such a quantitative measurement may be of use in the characterization of pathological neuropsychiatric states.

NR18 Tuesday, May 8, 11:30 A.M.

BENZODIAZEPINE RECEPTOR MEDIATED ANXIETY

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Summary:

The anxiolytic actions of benzodiazepines (BZD) have been attributed to the interaction of these compounds with high affinity, sterospecific receptors in the CNS. 3-Carboethoxy-β-Carboline (β-CCE) has a high affinity for BZD receptors and can antagonize the pharmacological actions of BZD in rodents. We have previously demonstrated that administration of β-CCE to rhesus monkeys elicits a profound behavioral syndrome reminiscent of "anxiety" accompanied by significant elevations in heart rate, blood pressure, plasma catecholamines and cortisol. The rise in plasma cortisol is preceded by an increase in plasma ACTH and β-endorphin, suggesting a specific activation of the hypothalamic-pituitary-adrenal axis. The antagonism of these effects by both diazepam (1 mg/kg) and the "pure" BZD antagonist Ro15-1788 (5 mg/kg) strongly suggests that β-CCE's actions are mediated through the BZD receptor.

To determine the interactions of various neurotransmitter systems in the β-CCE induced state of "anxiety", we pretreated the animals with various pharmacological agents. Clonidine (10 μg/kg) blocked the behavioral, physiological and endocrine effects of β-CCE (200 μg/kg). Propranolol (3 mg/kg) blocked the β-CCE induced rise in heart rate and blood pressure without blocking the increase in plasma catecholamines. Propranolol failed to completely block the behavioral, and did not block the endocrine effects of β-CCE. Cyproheptadine (1 mg/kg) blocked the β-CCE induced increases in plasma ACTH and cortisol, was unable to block the plasma catecholamine increases and partially blocked the behavioral effects of β-CCE. THIP (1 mg/kg) had some sedating properties, partially blocked the β-CCE induced behavior and failed to block the ACTH and cortisol rise.

Thus, β-CCE induced "anxiety" is completely blocked by diazepam and clonidine, the first by competition at the receptor level, the latter by pharmacological antagonism. Cyproheptadine blocked some components of the β-CCE induced state, as did THIP. These studies would suggest that the norepinephrine, serotonin and GABA systems are involved in the β-CCE induced state of "anxiety."

Poster Papers

NR19 Tuesday, May 8, 12 Noon-2:00 P.M.

PHARMACOTHERAPY AND EEG SLEEP IN DEPRESSION

James E. Shipley, M.D. (I), Sleep Evaluation Center, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213, D.J. Kupfer, M.D., D.G. Spiker, M.D., P.A. Coble, R.N. (I), V.J. Grochocinski, Ph.D. (I), Pittsburgh, PA

Summary:

In recent years, several theories such as the cholinergic hypersensitivity model (Sitaram and Gillin) and the two-process model of sleep regulation (Borbely) have been put forward to explain specific psychobiologic changes in depression, particularly EEG sleep alterations. In order to test hypotheses generated by these models, we have examined the effects of four antidepressant medications with presumed differing neurochemical profiles. Amitriptyline (AMI, n=16) is a tertiary amine with significant sedative and anticholinergic effects and mixed uptake blockade of biogenic amines. Nortriptyline (NOR, n=12) the secondary amine metabolite of AMI, as well as desipramine (DES, n=17) are primarily noradrenergic uptake inhibitors with less anticholinergic and sedative qualities. The investigational compound zimelidine (ZIM, n=13) is a potent and specific 5-HT uptake blocker which is not sedative and is nearly devoid of anticholinergic properties. To date, 58 inpatients with major depressive disorder have been studied in a 4-week randomized double-blind protocol which followed a 2-week drug-free washout period.

All four drugs had rapid and sustained effects upon sleep EEG. The drugs differed in their effects upon sleep continuity and architecture, as only AMI was associated with a consistently improved sleep continuity. In contrast, the patients treated with NOR and DES showed no improvement on sleep maintenance, while patients treated with ZIM showed poorer sleep continuity and a lightening of NREM sleep with continued administration, a feature also shared by DES. The effects of these drugs on REM sleep were more uniform as all four were associated with rapid and sustained suppression of several measures of REM sleep, with DES being the most potent and NOR the least. These results support the view that suppression of REM sleep appears to be a common effect of all antidepressants. Concerning the model of Sitaram et al., these data support the view that the cholinergic system is influential but not essential for REM sleep timing and intensity. Positive clinical response was associated with the presence of sedative qualities of the drug, a finding consistent with the two-process model of Borbely. In summary, antidepressant efficacy as deduced from EEG sleep studies in this group of moderate-to-severely depressed inpatients may be a function of an additive combination of sedative and REM suppressant effects.

NR20 Tuesday, May 8, 12 Noon-2:00 P.M.

REGIONAL CEREBRAL BLOOD FLOW IN A RAPID-CYCLING BIPOLAR PATIENT

Sukdeb Mukherjee, M.D., New York State Psychiatric Institute, 722 West 168th Street, Annex Room 422, New York, NY 10032, Isak Prohovnik, Ph.D. (I), Harold Sackeim, Ph.D. (I), Paolo Decina, M.D., Carl Lee, M.D. (I), New York, NY

Summary:

A 60 year old patient with rapid cycling bipolar I disorder (RDC) was followed through eight months of her illness and regional cerebral blood flow (rCBF) measurements were obtained during five separate manic episodes (three unmedicated and two medicated) and three normothymic periods (one unmedicated and two medicated). The course of illness was basically unmodified by pharmacotherapy with lithium carbonate, neuroleptics, carbamazepine, or combinations of the above. Cerebral blood flow measurements were performed with the Novo Cerebrograph model 32C using the 133-Xenon inhalation method and 32 detectors arranged in parallel (16 on each hemisphere).
Cerebral blood flow was higher during manic than normothymic phases and during medication-free than on-medication periods. Compared to normothymia, mania was associated with about a 30% flow increase off medication and about a 50% increase on medication. Compared to drug free periods, lithium and carbamazepine reduced flow by about 30% during normothymic and about 15% during manic periods. Evaluation of regional cerebral flow changes, contrasting manic to normothymia, showed the increase in global flow to be mostly accounted for by frontal lobe flow enhancements.

This is the first reported study of repeated measurements of cerebral blood flow during different mood states in a bipolar patient during multiple episodes of illness and remission. We are continuing with similar longitudinal studies using patients as their own controls and data from ongoing studies will also be presented.

NR21 Tuesday, May 8, 12 Noon-2:00 P.M.

PLASMA LEVELS OF AMOXAPINE AND CLINICAL RESPONSE

A. Ledesma-Jimeno, M.D., Department of Psychiatry, Hospital Salamanca, Gran Via 47-1, Salamanca, Spain 244217, J.F. Prieto Aguirre (I), A. Acosta-Lopez (I), A. Perez Urdaniz (I), J.R. Gutierrez Casares (I), M.A. Gonzalez Torres (I), Hurle Dominguez-Gil (I), Salamanca, Spain

Summary:

Twenty theree cases of depressive patients were studied. They were diagnosed following DSM-III criteria.All of them had a score above 20 points in the Hamilton Depression rating scale. Their ages were between 18 and 65 years old, and they were free of medication during the 2 weeks prior to the initiation of the treatment with Amoxapine. The day before the initiation of the treatment, the Dexamethasone Suppression Test (DST) was done following the Carroll norms. The Hamilton depression scale and the DOTES side effects scale were given the same day. The Hamilton and DOTES scales were administered again the days 7th, 15th and 21st after the initiation of the treatment with Amoxapine , and in the same day plasma levels of Amoxapine were performed plus 8.OH. Amoxapine and plus 7.OH. Amoxapine (gas-liquid chromatography with double derivatitation technique)

The Amoxapine was given in divided dosages 3 times a day, starting with 150 mg per day up to 300 mg. per day when its tolerance was good.

13 patients were non-suppressants to the DST, and 10 were suppressants. In the 10 non-suppressants it was observed in the 21st day and average improvement of 90%, while in the suppressants the average improvement was only of 40%. The best percentage of good therapeutic results (70% of the cases) was observed with plasma levels between 101 and 400 ng/ml of Amoxapine plus 8.OH. Amoxapine plus 7.OH. Amoxapine.

Regarding the side effects, 4 patients showed parkinsonism (slight akathisia, tremor, increase of muscle tonus) that was relieved with 7,5 mg/per day of Chlorhydrate of Triexiphenyl. One patient had to be excluded from the sample because of intense extrapiramidal symptoms; he had levels of Amoxapine plus 8.OH. Amoxapine plus 7.OH. Amoxapine of 438 ng/ml of which 308 were of 8.OH. Amoxapine, 9 ng/ml were of 7.OH. Amoxapine and 121 to Amoxapine (oral dose Amoxapine 300 mg/day). These results seem to confirm the Cohen and Harris hypothesis (1982) that Amoxapine has also neuroleptic action, which is attributed to the 7.OH. Amoxapine metabolite, noting that 600 mg of Amoxapine given orally can originate an amount of 7.OH. Amoxapine with a neuroleptic action equivalent to 6 mg of Butirophenone.

NR22 Tuesday, May 8, 12 Noon-2:00 P.M.

COMBINED THERAPY WITH LITHIUM AND CARBAMAZEPINE

Akira Kishimoto, M.D., VA Medical Center, 3801 Miranda Avenue, Palo Alto, CA 94304, Fumiaki Omura, M.D. (1), Palo Alto, CA; Yoichi Umezawa, M.D. (1), Shimane, Japan; Etsuo Fukuma, M.D. (1), Tottori, Japan

Summary:

Combined therapy with lithium (Li) and carbamazepine (CBZP) for the prevention of affective episodes was studied in 17 patients with either bipolar I or bipolar II disorder (RDC). All patients had previously been treated with Li alone with an inadequate response and 9 had also failed to respond to CBZP alone. The duration of the combined therapy ranged from 18 to 120 months (mean 52.5 months). The frequency of affective episodes during the combined therapy was significantly less than that experienced during the control period ($p<0.001$), that is, before patients had been treated prophylactically either with Li or CBZP. It was also significantly less ($p<0.01$) than during the preceding trial with Li alone. Not only were the episodes less frequent with combined therapy, but the severity of symptoms was also less than when prophylaxis was accomplished with Li alone. Nine patients had received Li alone, CBZP alone or the combined therapy. Eight of these patients were better on the combination than on either other treatment; none was worse. During the period of combined treatment, plasma Li levels were low; no noteworthy side effects were observed. Combined therapy with Li and CBZP provided superior maintenance treatment for patients resistant to treatment with Li or CBZP alone.

NR23 Tuesday, May 8, 12 Noon-2:00 P.M.

CROSS CULTURAL PHARMACOKINETICS OF DESIPRAMINE

Edmond H. Pi, M.D., Department of Psychiatry, Medical College of Pennsylvania/EPPI, 3200 Henry Avenue, Philadelphia, PA 19129, George M. Simpson, M.D., Philadelphia, PA; Thomas B. Cooper, M.A. (I), Orangeburg, NY

Summary:

The variation in pharmacokinetics of certain drugs in different ethnic groups has been suggested to be the result of the differences in the rate of drug metabolism and volume of drug distribution. These factors appear to be mainly determined by genetic predisposition but influenced by environmental factors such as exposure to chemical agents and diet. In the case of tricyclic antidepressants, anecdotes and clinical reports claim that Asian patients require lower doses than Caucasians, with a ratio of 1:2. One study reported that total clearance of DMI was significantly more rapid in Caucasians than in Chinese. Questions regarding such psychopharmacokinetic and dosage differences in these two ethnic groups still remain unclear. Twenty healthy volunteer subjects who are direct Asian descendants (Chinese/Japanese/Korean) ingested a single dose of 50 mg desipramine (DMI) after fasting for at least 10 h. Blood and saliva samples were collected at 1,3,5,7,12 and 24 h post-dose. Plasma and saliva concentrations of DMI were assayed in duplicate using a gas chromatographic-nitrogen detector procedure. The results then were compared with the results generated from a prior study of 20 healthy Caucasian volunteer subjects who ingested a single dose of 75 mg DMI. In this comparison of a single-dose study in the two groups, there were no significant differences in the following pharmacokinetic parameters: C_{max} (peak serum concentration), V_d (Volume of drug distribution), plasma clearance, elimination half-life and C_{max} normalized to 1 mg/kg. The only statistically significant finding was that T_{max} (time of peak serum concentration) was earlier in the Asian than in the Caucasian group. Plasma samples were also analyzed for the presence of hydroxylated DMI but this was present in insufficient amounts for pharmacokinetic analyses. The saliva/plasma ratios were compared in two groups but no significant differences were found. Our data suggest that there are no significant pharmacokinetic differences in these two ethnic groups using plasma concentration measurements after a single dose of DMI ingestion during a 24 h post-dose period. The pharmacokinetic and clinical implications of these results will be discussed.

NR24 Tuesday, May 8, 12 Noon-2:00 P.M.

CALCIUM RELATIONSHIPS TO SEVERITY OF DEPRESSION

Lena G. Huang, M.D., Department of Psychiatry, University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78284, Charles Bowden, M.D., Martin Javors, Ph.D. (1), Joe Johnson, M.D., San Antonio, TX

Summary:

Study of possible disturbances of calcium metabolism in affective illnesses has a long, and recently more active history. Increased plasma and CSF calcium may be associated with some depressive states, and red blood cell (RBC) Ca^{2+} ATPase may be altered in affective disturbances. In the main however, studies to date are inconclusive and even contradictory. We studied the relationship of several measures of calcium function to overall severity of illness in patients with primary depression, unipolar or bipolar type, diagnosed by Research Diagnostic Criteria (RDC) based on the Schedule for Affective Disorders and Schizophrenia (SADS) diagnostic interview. All patients were evaluated after a 7 to 10 day drug free period, while on a low calcium low monoamine diet. Severity of illness was based on the Global Assessment Scale (GAS) from the SADS. Calcium related determinations were of plasma, CSF and platelet calcium, RBC Ca^{2+} ATPase, and calcium uptake into platelet membranes. The relationship of these measures to the GAS score was assessed by Pearson product moment correlation coefficient.

Results. Among the 27 unipolar patients a higher calcium uptake was associated with greater severity of illness. This was significant for both ATP stimulated calcium uptake and total calcium uptake, both with and without added calmodulin. By contrast, no significant calcium uptake relationships with severity were present in the 9 bipolar depressed patients studied to date. For RBC Ca^{2+} ATPase, a lower ATPase value was associated with greater severity of illness in bipolar, but not unipolar depressed patients, a result consistent with that reported by Linnoila, et al. (Arch. Gen. Psychiat. 40:1021, 1983). No significant association of plasma, CSF or platelet calcium with severity of illness was present for unipolar or bipolar patients, or for the two groups analyzed together.

These results are consistent with other evidence that calcium function may be disturbed in subgroups of depressed patients. Furthermore, these results, and related data to be presented, suggest that unipolar patients may differ significantly from bipolar patients on several of these measures of calcium function.

NR25 Tuesday, May 8, 12 Noon-2:00 P.M.

ENHANCED PILOCARPINE MIOSIS IN DEPRESSED PATIENTS

Surendra Kelwala, M.D., Department of Psychiatry, VA Medical Center, Allen Park, MI 48101, Don Jones, M.D. (I), Jessie Bell, Ph.D. (I), Natraj Sitaram, M.D. (I), Detroit, MI

Summary:

A number of studies have linked depressive mood and behavior with hyperresponsive cholinergic system. In view of these links between acetylcholine and depression it is of interest to identify reliable behavioral and physiological endpoints that can be used as *in vivo* markers of cholinergic activity in depressed and normal people. Human iris musculature's response to cholinergic agents, observed by measuring changes in pupil diameter, shows excellent dose-dependency, specificity and test-retest reliability. Using a highly sensitive binocular television pupillometer and making corrections for intrinsic variability of baseline pupil diameter, we measured the pilocarpine (0.125%) induced miotic response in 26 depressed, 19 normal, and 7 non-affective psychiatric subjects. Miotic response in depressed patients was significantly ($p < .001$) higher than in controls. To ascertain the pharmacological specificity of pilocarpine action we also studied the mydriatric response to phenylephrine (2.5%) and hydroxyamphetamine (0.5%) in depressed and normal subjects. There were no significant differences between the mydriatic response of depressed and normal controls. Since pilocarpine is a direct cholinergic agonist the results are indicative of hypersensitive muscarinic receptor state in depression. Technique of pupillometry and implications of these findings regarding cholinergic-adrenergic models of depression will be discussed.

NR26 Tuesday, May 8, 12 Noon-2:00 P.M.

ANTIDEPRESSANT WITHDRAWAL AND HYPOTHALAMIC-PITUITARY-ADRENAL REGULATION

Steven C. Dilsaver, M.D., University of Michigan Medical Center, Department of Psychiatry, Ann Arbor, MI 48109, John F. Greden, M.D., Ann Arbor, MI

Summary:

Withdrawal of antidepressant medications may be an important source of variance in hypothalamic-pituitary-adrenal (H-P-A) feedback regulation. If so, the length and type of drug withdrawal would be important variables in all research procedures studying H-P-A measures. We investigated the effects of antidepressant withdrawal by serially measuring post-dexamethasone plasma cortisol concentrations and matched clinical ratings in 15 patients withdrawan from tricyclic antidepressants during the first two weeks of hospitalization. Our control group consisted of nine endogenously depressed patients who were drug free at time of hospitalization (14 days elapsed since last dose of psychotropic medication). All patients and controls were hospitalized in the Clinical Studies Unit and diagnosed using SADS and RDC as having major depressive disorder, endogenous subtype. Diagnosticians were blind to H-P-A measures and blind raters completed the Hamilton Rating Scale for Depression weekly. Post-dexamethasone cortisol concentrations were significantly higher during the drug withdrawal phase. Twelve of the experimental group had higher post-dexamethasone cortisol levels during the withdrawal phase than the post-withdrawal phase ($p=0.0033$, $t=3.23$, 13DF, paired t-test, one tailed). Ten of 14 (71.4%) of the withdrawal subjects had a positive DST during the 14 day withdrawal period compared to 2 of 9 (22.2%) of the control subjects ($p=0.03$, Fisher's Exact) during a comparable two week period. These differences in the frequency of positive DSTs and post-dexamethasone cortisol levels were not present when the withdrawal patients had become drug free. Changes in severity or weight did not account for the results. These preliminary data are consistent with the hypothesis that withdrawal of antidepressants having anticholinergic properties may induce hypothalamic-pituitary-adrenal dysregulation secondary to cholinergic overdrive.

NR27 Tuesday, May 8, 12 Noon-2:00 P.M.

CLINICAL USE OF THE DEXAMETHASONE SUPPRESSION TEST

Roger F. Haskett, M.B.B.S., Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109, Athanasios P. Zis, M.D. (I), A. Ariav Albala, M.D., Ann Arbor, MI; Bernard J. Carroll, M.D., Durham, NC

Summary:

Many clinicians include the Dexamethasone Suppression Test (DST) in the diagnostic evaluation of certain patients. Interpretation of test results from inpatients may be influenced by nonspecific factors associated with the first few days of hospitalization. This study examined the diagnostic confidence and test-retest reliability of the DST in 95 patients admitted to a general psychiatry unit with prominent symptoms of altered mood. We compared the results from an "admission" DST, completed during the first two days of hospitalization, with results from a DST repeated 7-21 days after admission and ≥7 days after complete withdrawal from medication. Patients <80% of ideal body weight or with physical illness known to affect the DST were excluded.

We found that: 1) 70% of patients with an RDC diagnosis of Major Depressive Disorder-endogenous subtype (MDD-E) had an abnormal DST on admission compared to 60% on repeat. 2) 28% of patients with a depressive disorder other than MDD-E had an abnormal DST on admission compared to 12% on repeat testing. 3) Diagnostic confidence of an abnormal DST in patients with depressive disorder was 80% on admission and 88% on repeat testing. 4) The DST result was unchanged at repeat testing in 78% of patients with endogenous depression and in 76% of patients with other depressive disorders. 5) The incidence of abnormal DST results also decreased between admission and repeat testing in patients with mania (36% to 18%), schizoaffective disorder (59% to 41%), and schizophrenia (100% to 0%). The DST result altered between testing in 48% of these patients.

Mean post-dexamethasone cortisol levels for each diagnostic category decreased between admission and repeat testing. Change in post-dexamethasone cortisol values was significantly correlated with change in Hamilton Depression score in only the patients with nonendogenous depression and did not significantly correlate with weight change for any diagnostic group.

These data indicate that the diagnostic confidence of an abnormal DST in patients with a depressive disorder is increased slightly after a medication-free period in hospital. Weight change after admission does not appear to be related to changes in DST results.

NR28 Tuesday, May 8, 12 Noon-2:00 P.M.

BASAL CORTISOL LEVEL RELATION TO DIAGNOSIS AND DST

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Summary:

As part of the NIMH Clinical Research Branch Psychobiology of Depression Program - Biological Studies, we examined the sensitivity and specificity to major depressive disorder of elevation of pretreatment, basal (pre-dexamethasone) measures of adrenocortical activity, and related these to results obtained with a 1 mg overnight dexamethasone suppression test (DST).

Methods: 132 patients admitted for treatment of depression (85 unipolar, 47 bipolar) and 80 age-matched healthy controls (33 hospitalized) were studied after a 9 day drug washout interval. Basal measures of 8:30 a.m. and 10 p.m. plasma cortisol (PC), CSF cortisol and 24 hour urine free cortisol (UFC), and post-DST a.m. PC, were collected during study days 10 - 13.

Results: Mean a.m. PC, CSF cortisol and UFC (but not p.m. PC), as well as post-DST a.m. PC, were significantly higher in depressed patients than healthy controls. The diagnostic predictive value of elevation of each cortisol measure was computed as % of elevated observations which derived from depressed patients in a sample of 50% depressed and 50% healthy controls ("PV50"). The criteria defining elevation were chosen to maximize PV50 for each cortisol measure. Higher levels of diagnostic confidence in distinguishing depressed patients were obtained when elevation of basal UFC or basal CSF cortisol was used (PV50=89% and 82%) as compared to post-DST a.m. PC $\geq$ 5 µg/dl (PV50=75%). The sensitivity in depressed patients of elevation above these criteria was 34% for UFC $\geq$ 150 µg/day and 45% for CSF cortisol $\geq$ 10 ng/ml, higher than the 32% sensitivity of post-DST a.m. PC $\geq$ 5 µg/dl.

Point biserial correlations of all basal measures with post-DST a.m. PC level were run, treating this as a dichotomous measure (suppressing to 5 µg/dl or not). The 3 measures with highest correlations were a.m. PC (r=.41, n=107), p.m. PC (r=.38, n=103) and UFC (r=.34, n=87). We used a stepwise logistic regression procedure to predict post-DST a.m. PC suppression or non-suppression on the basis of these 3 measures. The result obtained was statistically much better than chance (96% or 130/135 suppressors correctly identified). However the procedure did not predict DST nonsuppression with much practicality (11/37 nonsuppressors correctly identified).

We conclude: (1) There is significant relation of measures of basal adrenocortical function to dexamethasone response. However DST nonsuppression cannot thus far be practically predicted from these basal measures. (2) Elevation of basal adrenocortical function as measured by UFC and CSF cortisol is as or more specific to depressive illness than is DST nonsuppression. This implies that basal UFC level could be a practical substitute for DST response in studies of repetitive measures of adrenocortical function and clinical state. For example, basal UFC level warrants further study as an indicator of ongoing treatment response.

NR29 Tuesday, May 8, 12 Noon-2:00 P.M.

CORRELATES OF MARKED NON-SUPPRESSION

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Summary:

Because of continuing evidence that DST non-suppression occurs in a variety of diagnostic classes, we have explored neuroanatomic, physiologic, and behavioral correlates of marked cortisol resistance to dexamethasone utilizing a high risk strategy with pituitary adrenal disinhibition as the independent variable. Thus far, 400 patients have completed the DST. Of this sample, 28 patients had a 4:00 p.m. post-dexamethasone cortisol value that was greater than 2 standard deviations from the mean, i.e., 4:00 p.m cortisol $\geq$ 14.94 µg./dl. Clinical and physiologic factors that distinguish this group from individuals showing normal suppression and/or lesser degrees of non-suppression will be presented. Of particular interest is the positive relationship between post-dexamethasone cortisol value and ventricular brain ratio. Suppressors, non-suppressors, and a group of age- and sex-matched normal controls, differed significantly from each other in VBR, ($p < .01$). Furthermore, VBR was found to correlate significantly and independently in a negative direction with assessments of orientation, calculation, short-term memory, and judgment of similiarities. These findings are of particular interest in view of a recent report documenting a relationship between cortisol hypersecretion and increased ventricular size, and studies of similar phenomena in patients with Cushing's syndrome. The possibility that cortisol dysfunction might serve as a marker of early damage to periventricular control loci in certain individuals will be discussed.

NR30 Tuesday, May 8, 12 Noon-2:00 P.M.

THE DST AND PITUITARY-ADRENOCORTICAL FUNCTION

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Summary:

A substantial subgroup of depressed patients (pts) and perhaps some with other psychiatric diagnoses (dx) as well have, during their illness, a sustained increase in pituitary-adrenocortical (PAC) activity. It's important for research and may in the future be important for clinical purposes to accurately identify such pts. The 1 mg overnight DST, a modification of which is now widely used to assess PAC activity in psychiatric pts, was originally intended and is now used in endocrinology as a screening test to rule out, with normal suppression, the PAC hyperfunction of Cushing's syndrome. Nonsuppression is not considered diagnostic but indicates only the need for further PAC evaluation. A modified 1 mg DST, however, is now used in psychiatry to identify both normal and "abnormal" PAC regulation. Recent studies with this DST report a substantial rate of nonsuppression in both healthy people (up to 19%) and in pts with diverse psychiatric and physical conditions. Does the 1 mg DST identify pts with meaningful differences in PAC function? We have compared the results of 1 and 2 mg DSTs to baseline 24 hour urinary cortisol (UC), a specific and sensitive indicator of sustained PAC activity.

Fifty-six psychiatric inpts, 17 men and 39 women, with a mean age of 41 had a 24 hr urine collection, then took 1 or 2 mg of dex and had blood sampled at 4 and 11 p.m. the next day. Unselected for dx, 25 had major depression; the others a variety of dx. Serum and UC were measured by RIA with any serum C > 4.0 ug% defining nonsuppressors (NS) and 90 ug/24 hrs the upper limit of normal for UC.

For the 1 mg DST pts the 10 NS and 13 S did not differ significantly in mean baseline UC (74.1 vs 60.4 ug/24 hrs) or in the portion with elevated (> 90 ug/24 hrs) UC (10% vs 23%). But with the 2 mg DST the 7 NS as compared to the 26 S had substantially and significantly higher mean UC (140.7 vs 66.2 ug/24 hrs, $t = 2.47$, $p < .01$) and a higher portion with elevated UC (71% vs 18%, $x^2 = 7.11$, $p < .01$).

These data suggest that the 1 mg DST, as commonly carried out in psychiatric settings, does not separate patients with and without definitive PAC hyperfunction. Yet nonsuppression after a 2 mg dex dose is clearly associated with PAC hyperfunction. These observations, along with those of related studies, suggest that the DST, as commonly done in psychiatric settings, is not suitable for identifying the heuristically important subgroup of psychiatric patients who have a clear disturbance in PAC function.

NR31 Tuesday, May 8, 12 Noon-2:00 P.M.

DEXAMETHASONE SUPPRESSION TEST AND MANIC RELAPSE

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Summary:

Recent reports indicate that the DST is abnormal in a significant number of cases of mania. In an ongoing study of acute mania which includes the DST we tested the hypothesis that the DST is a state marker in mania, as it has been shown to be in melancholia, and that failure of an abnormal test to convert with treatment indicates incomplete treatment and high risk of early relapse. We present preliminary results which suggest that this hypothesis is correct.

Eighteen patients diagnosed by DSM-III criteria as bipolar, manic, who were DST non-suppressors on admission were re-tested prior to discharge when they were felt to be in clinical remission. The 1 mg overnight DST, as standardized by Carroll, was used at both admission and discharge. The medical exclusion criteria of Carroll were utilized. Cortisols were measured by radioimmunoassay and a post-dexamethasone 4:00 p.m. or 11:00 p.m. cortisol value greater than 5.0 mcg/dL was considered abnormal. The repeat tests were done in the week prior to discharge when in the opinions of the treating resident and attending psychiatrists the patients were stable. Discharging physicians were blind to the results of the repeat DST.

Fourteen patients converted to normal suppression on repeat testing while 4 patients had persistently abnormal tests. One converter was lost to follow-up. Two converters were rehospitalized for mania 3 and 4 weeks after discharge, respectively. Both admitted to non-compliance with discharge medication. The remaining 11 converters have remained well (not rehospitalized or requiring medication change or adjustment) for outpatient follow-up periods ranging from 4 to 15 months.

Three of the 4 patients with persistently abnormal tests were rehospitalized for mania, 3, 6, and 14 days after discharge, respectively. Two had been compliant with discharge medication while one had not. The fourth non-converter became depressed immediately following discharge and was treated as an outpatient with a tricyclic antidepressant in addition to his maintenance lithium.

Definitive conclusions are impossible to draw due to the small size of our study population but the results suggest that the DST is a state marker in mania and that non-conversion of an abnormal test indicates incomplete resolution of a manic episode.

NR32 Tuesday, May 8, 12 Noon-2:00 P.M.

DST IN GERIATRIC DEPRESSION AND DEMENTIA

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Summary:

Abnormal dexamethasone suppression test (DST) has been reported in depression and represents a disinhibition of the hypothalamic pituitary adrenal axis secondary to brain neurotransmitter abnormalities. Clinical reports suggest that DST may be helpful in differentiating depression with reversible dementia (DRD), often called pseudodementia, from established organic mental disorders. However, in a preliminary report a significant percentage of patients with Alzheimer's disease had an abnormal DST. We studied a large number of geriatric patients and hypothesized that DST would 1) differentiate depression from primary degenerative dementia, and 2) distinguish patients with depression and dementia who improve cognitively when their affective symptoms subside from those who remain cognitively impaired.

The subjects were 126 geriatric psychiatric patients. Diagnosis was made according to Research Diagnostic Criteria (RDC) and DSM III. Depressive symptoms were quantified with the 24-item Hamilton Depression Rating Scale (HDRS) and cognitive symptoms with the Minimental State (MMS). Family history was classified according to Family History RDC. Patients with major depression and dementia whose cognitive impairment improved (ΔMMS $\geq$ 3, final MMS $\geq$ 24) when symptoms of depression subsided (ΔHDRS $\geq$ 10 or final HDRS $\leq$ 12) were classified as DRD. Patients who met criteria for major depression and dementia and remained demented (MMS $<$ 24) even when depressive symptoms improved (ΔHDRS $\geq$ 10, final HDRS $\leq$ 12) were considered to have an established organic mental disorder in addition to depression (DD). Abnormal DST (1 mg) was found in 34.1% of primary degenerative dementia patients (N=41) and in 70.6% of all patients with major depression (N=85), a significant difference (x^2=12.95, df=1, $p < .001$). There was no association between abnormal DST and severity of depressive symptoms in either patients with primary degenerative dementia or major depression. DRD patients (N=26) had abnormal DST (76.9%) more frequently than patients with primary degenerative dementia (x^2=9.99, df=1, $p < .005$). However, DRD patients had abnormal DST at a similar frequency (76.9%) with those with DD (N=43) (68.7%) and with depressives who never had a dementia syndrome (N=43) (67.4%).

We conclude that abnormal DST is not useful in differentiating DRD from DD, a frequent clinical problem. The presence of abnormal DST in primary degenerative dementia suggests that a subgroup of patients with this disorder may have a brain neurotransmitter dysfunction similar to that of depressed patients.

NR33 Tuesday, May 8, 12 Noon-2:00 P.M.

IS RAPID EYE MOVEMENT LATENCY CONCORDANT IN DEPRESSED RELATIVES?

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Summary:

There is evidence of genetic influence on sleep architecture in animals and humans. Sleep architecture by the polysomnogram (PSG) is abnormal in many depressions. We hypothesize that PSG parameters are consistent among first-degree family members with depression.

We have studied 8 first-degree relative pairs when each was depressed and medication-free. Subject pairs were grouped by categorical consistency between REM latencies (RLs); RL's $\leq$ 65.0 minutes were categorized as "low". Subjects were diagnosed unipolar or bipolar and endogenous or nonendogenous by RDC.

		Diagnosis: Same	Diagnosis: Different
REM Latency	Same	6	0
	Different	0	2

The data are presented above. Six of eight pairs showed RL categorical consistency. All subject pairs with the same diagnosis had categorically similar RLs. For the two discrepant pairs, one patient had Bipolar Endogenous depression, while the sibling had Unipolar Nonendogenous depression.

The relevance of these findings in the genetics of depression will be discussed.

NR34 Tuesday, May 8, 12 Noon-2:00 P.M.

METABOLISM AFFECTS CLINICAL RECOVERY IN ANOREXIA

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Summary:

Physiologic factors may be contributory to recurrent weight loss in anorexia nervosa. In the weeks immediately after weight restoration anorectics require a greater than normal caloric intake to maintain their weight. This suggests that an alteration in energy balance occurs after weight recovery.

9 women with anorexia nervosa participated in a weight restoration program on an inpatient ward at NIMH. After weight recovery (45.1 $\pm$ 1.2 kg) subjects were required to maintain a stable weight ($\pm$ 0.5 kg) for a month after weight recovery and caloric intake was measured. Patients were observed as necessary to avoid binging and purging. Mean $\pm$ SEM caloric intake for anorectics for 4 days was 2154 $\pm$ 57 kcal/day or 48.0 $\pm$ 1.8 kcal/kg/day, significantly different ($p < .01$) then 11 healthy control (57.4 $\pm$ 2.2 kg) women who consumed 1768 $\pm$ 115 kcal/day, or 31.1 $\pm$ 2.0 kcal/kg/day.

Animal studies suggest that endocrine and catecholamine systems, and activity levels can contribute to alterations in energy efficiency. Disturbances in gonadal, cortisol, vasopressin, and thyroid systems are present after weight recovery in anorexia nervosa. Although norepinephrine (NE) and NE metabolites concentrations are normal in short term weight recovered anorectics, after clonidine challenge, a down regulation of α_2 adrenergic receptors in this group of anorectics suggests altered adrenergic functional activity. Using activity monitors, this group of anorectics has more than twice the activity counts as controls. Any or all of these abnormalities could account for the inefficient use of energy in short term weight recovered anorectics.

In contrast, we found a group of long term weight recovered anorectics (20 $\pm$ 7 months) had a normal caloric intake, as well as normalization of many neuroendocrine disturbances and activity levels. However, while α_2 adrenergic receptor activity was similar to controls, a significant ($p < .05$) decrease in CSF and plasma levels of NE and NE metabolites had occured, suggesting a resetting of adrenergic tone. Since these studies were cross sectional in design it is unknown whether anorectics with good prognosis differ in adrenergic regulation from those that do poorly, or whether alterations need to occur in adrenergic function to allow weight maintenance to be more easily accomplished. Altered energy balance in short term weight recovered anorectics is clinically critical because it implies that treatment and weight maintenance need to be extended beyond immediate recovery.

NR35 Tuesday, May 8, 12 Noon-2:00 P.M.

DEXAMETHASONE SUPPRESSION TEST AND WEIGHT LOSS

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Summary:

There is concern that DST nonsuppression in patients with major depression may be a function of the weight loss that is often part of the depressive illness. The value of the DST as a biological tool in the assessment of patients with major depression may be seriously compromised if DST results are shown to be strongly affected by weight loss. In order to assess the impact of weight loss on DST results, we compared rates of DST nonsuppression in 32 psychiatric inpatients with weight loss, to 32 psychiatric inpatients without weight loss, matched (blindly on DST status) for age, sex and diagnosis.

Forty-two subjects received a 1 mg DST, 10 males and 32 females. The index group reported a weight loss of 5 to 44 lbs prior to hospitalization. Forty of these subjects had major depression and 2 schizophrenia. Twenty-two subjects received a 2 mg DST, 8 males and 14 females. This index group reported a weight loss of 5 to 25 lbs prior to hospitalization. Twelve subjects had major depression, 2 atypical depression, 2 schizophrenia, 2 brief reactive psychosis and 4 adjustment disorder. The extent of weight loss was assessed by a questionnaire at the time of admission. Whether a 1 or a 2 mg DST was given was a matter of chance. Patients received the dexamethasone orally at midnight, and blood samples were drawn at 4:00 and 11:30 p.m. the following day. Serum cortisol concentration was determined by radioimmunoassay. A cortisol level of 5 mg/dl in either the 4:00 or 11:30 p.m. samples signified nonsuppression. Each patient received a DSM-III diagnosis from one of two attending psychiatrists without knowledge of DST results.

Of the 21 subjects in the 1 mg group with weight loss, 10 (48%) were found to be nonsuppressors. In the matched group, 10 of the 21 (48%)were also nonsuppressors. The rate of nonsuppression was not affected by whether the weight loss was greater or less than 20% of body weight. Of the 11 subjects in the 2 mg group with weight loss, 2 (18%) were nonsuppressors. In the matched group 3 (27%) of the 11 were nonsuppressors. The differences between the groups were not significant. We have been unable to show a significant effect of weight loss on nonsuppression rates in a matched group of psychiatric inpatients with either a 1 or a 2 mg DST.

NR36 Tuesday, May 8, 12 Noon-2:00 P.M.

DEXAMETHASONE SUPPRESSION TEST IN STRESSED NORMALS

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Summary:

Many recent studies have questioned the specificity of the Dexamethasone Suppression Test as a marker for depression, and these and older studies have raised the issue of whether cortisol hypersecretion and dexamethasone resistance relate more to stress effect than to psychiatric diagnosis. The authors studied pre- and post-dexamethasone cortisol secretion in 52 healthy, young, nondepressed (mean Beck score 5.3) housestaff officers under the considerable stress of residency training at a high pressured academic center. All subjects were studied around a night on-call, which typically involved heavy work-load with critically ill patients and substantial sleep deprivation. In addition to Beck Inventory, subjects completed visual analogue scales rating stress, mood and anxiety.

Results:

1. The frequency of dexamethasone nonsuppression at 4pm (>5μg/dl) was 3/52 (5.8%). Two nonsuppressors were "early escapers" (suppressed at 8am); the third nonsuppressor was not studied at 8am.
2. Baseline (predexamethasone) 4pm hypercortisolemia >12μg/dl occurred in 8/52 (15.4%) subjects. Additional borderline 4pm hypercortisolemia ≥7-12μg/dl occurred in 27/52 (51.9%) subjects.
3. 2/3 nonsuppressors had predexamethasone 4pm cortisols of >12μg/dl.
4. 1/3 nonsuppressors reported recent weight loss. 3/8 subjects with baseline hyper-cortisolemia reported recent weight loss. 48% of total sample reported some recent weight loss (range 3-15 lbs.).
5. Average predexamethasone 4pm cortisol values were significantly greater with high vs low level of perceived stress and anxiety: 7.3 vs 9.7μg/dl ($t=2.97$, $df=50$, $p=<.005$); and 7.7 vs 9.3μg/dl ($t=1.98$, $df=50$, $p<.05$) respectively. However there was no significant difference with high vs low perceived mood.

In a healthy, nondepressed, but stressed, young adult population, baseline hyper-cortisolemia associates with increased perceived stress as compared with reference cortisol concentrations in nonstressed normals. However, dexamethasone suppression is observed in normal frequency. Our data does not find that minor weight loss affects baseline cortisol concentrations or dexamethasone suppression. (Supported by NIMH grant 2R01-MH12464-10 PES.)

NR37 Tuesday, May 8, 12 Noon-2:00 P.M.

SERIAL DST'S IN DEPRESSED PATIENTS AND CONTROLS

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Summary:

The value of endocrinologic parameters for diagnosis and prediction of course and treatment-response in depressive illness is evaluated in an ongoing longitudinal study with DST's, TRH-tests, prolactin, and growth-hormone measurements in series. Results concerning the DST are presented. Weekly DST's were performed in 25 hospitalized depressed patients and 12 schizophrenic and manic controls with both suppression and non-suppression at initial evaluation. The cortisol levels were related to clinical course and body weight. A cut-off point was established by DST results in 35 healthy controls. In 15 healthy volunteers the DST was repeated under psychological stress.
The main results are as follows:
- The depressed non-suppressors usually had progressive normalization of their DST-response in conjunction with clinical improvement, the DST-normalization closely coinciding with clinical response.
- Single switches from non-suppression to suppression and from suppression to non-suppression occurred in a number of depressed patients without simultaneous or following change in clinical state.
- Abnormal DST-results are also seen in schizophrenic and manic patients, especially immediately after hospitalization.
- Even slight stress can cause abnormal DST-results in healthy volunteers.
The results will be discussed emphasizing the question whether an abnormal DST is attributed to non-specific stress or to a neurotransmitter disturbance specific for depression.

NR38 Tuesday, May 8, 12 Noon-2:00 P.M.

IMPAIRED OPIOID-ENDOCRINE REGULATION IN DEPRESSION

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Summary:

Forty-two drug-free adult psychiatric inpatients (24 of which met RDC criteria for major depressive disorder) and 14 healthy volunteers received 5 mg morphine intravenously at 9:30 a.m. Blood samples were drawn via an intravenous catheter immediately before and at 30 minute intervals for three hours following the injection. In twelve of the subjects the experiment was repeated within 48 hours with placebo. A Dexamethasone Suppression Test (DST) was performed within 72 hours of the morphine infusion.

Morphine markedly suppressed cortisol secretion. The decline of cortisol values was progressive and at a rate approximating the half-life of cortisol in 48 of 56 subjects. In eight patients the progressive decline in cortisol values was interrupted by an unambiguous increase indicating spontaneous resumption of cortisol secretion. Seven of these eight patients met criteria for major depression. Comparison of DST results to the effect of morphine on cortisol secretion revealed that early resumption of cortisol secretion was also associated with abnormal DST results. In two patients, the morphine infusion and the DST were repeated following a course of ECT. Clinical recovery was associated with normalization of cortisol response to both morphine and dexamethasone.

In a separate experiment involving fourteen additional patients and four healthy volunteers, we studied the effect of 2.5 mg morphine on cortisol secretion. Morphine suppressed cortisol secretion and early resumption of cortisol secretion was associated with abnormal DST results.

These results provide support for the presence of an inhibitory opioid mechanism on the human hypothalamic-pituitary-adrenal (HPA) axis. More important they indicate that an impairment in this inhibitory mechanism is associated with a diagnosis of major depression and impaired glucocorticoid feedback, i.e. abnormal DST results.

These observations suggest that an opiate-endocrine dysregulation may be responsible for the increased activity of the HPA axis observed in depression.

NR39 Tuesday, May 8, 12 Noon-2:00 P.M.

CORTISOL SUPPRESSION INDEX IN DST INTERPRETATION

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Summary:

The dexamethasone suppression test (DST) has been considered a useful biologic state marker of depression. A 4 p.m. or 11 p.m. postdexamethasone plasma cortisol concentration greater than 5.0 mug/dl detects about two-thirds of depressed patients. We have previously suggested use of a cortisol suppression index (CSI), the ratio of pre- to post dexamethasone plasma cortisol concentrations, to make the DST more practical for outpatient use.

Our objective in the present study was to prospectively evaluate the usefulness of the CSI in a larger sample of depressed and nondepressed patients. We compared sensitivity and specificity rates obtained with an 8 a.m. CSI, 4 p.m. CSI, and Carroll criteria.

25 inpatients with a major depressive disorder had a mean 8 a.m. CSI of 4.80 ± 3.30 (SD) and mean 4 p.m. CSI of 3.02 ± 3.32 (SD). 23 inpatients with other psychiatric diagnoses had a mean 8 a.m. CSI of 8.61 ± 4.17 (SD) and a mean 4 p.m. CSI of 6.79 ± 3.80 (SD). These results were statistically significant at 8 a.m. ($t=4.80$, $df=43$, $p<.001$) and 4 p.m. ($t=3.48$, $df=43$, $p<.01$).

An 8 a.m. CSI below 7.0 and 4 p.m. CSI below 2.5 provided the most sensitive and specific criterion values for diagnosis of a major depressive disorder. These values yielded sensitivity rates of 88% (8 a.m.) and 73% (4 p.m.) and specificity rates of 85% (8 a.m.) and 91% (4 p.m.). These results compared favorably to those we obtained using Carroll's criteria (76% sensitivity; 78% specificity).

Our data suggest use of a cortisol suppression index may serve as a useful alternate interpretation of the DST. A larger sample and additional control groups are needed to establish definitive CSI criteria to optimize sensitivity and specificity.

NR40 Tuesday, May 8, 12 Noon-2:00 P.M.

IMIPRAMINE-LIKE EFFECTS OF ESTROGEN ON SEROTONIN UPTAKE

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Summary:

Estrogen has been reported to have some antidepressant-like effects in both clinical and experimental paradigms, and has been known to reverse the abolishment of imipramine-induced, down-regulated cortical serotonin$_2$ receptors occuring after ovarectomy. The exact mechanisms for these antidepressant effects of estrogen, however, have not been entirely understood. To examine the effects of estrogen on serotonin (5HT) physiology in human subjects, we kinetically studied the in vitro effects of B-estradiol on platelet serotonin uptake in normal volunteers. Analysis of variance on data from ten experiments indicated that B-estradiol's effect on platelet serotonin uptake was much like imipramine in that it significantly decreased platelet affinity for serotonin ($F = 19.7$, $p < .002$) without significantly changing the maximum velocity of uptake. The inhibitory effects on uptake were milder than imipramine at micromolar concentrations of estradiol. A twenty percent inhibition was found at 10-6 M B-estradiol compared to the fifty percent inhibition cited for similar concentrations of imipramine. At lower concentrations of estrogen (10 -8 M), a similar degree of inhibition was found, although the competitive effect could be more easily overcome by increasing the concentration of substrate (serotonin), at those lower concentrations of estrogen.

These results agree well with new data obtained from measurement of platelet serotonin uptake across the menstral cycles of women volunteering with menstrually-related variations in mood. In five women studied twice weekly there was a follicular trough in platelet serotonin affinity, concurrent with the expected increase in estrogen occuring during that phase of the menstrual cycle. The results would indicate that estrogen may have an endogenous imipramine-like effect, decreasing plasma cell membrane affinity for serotonin transport intracellularly. Insofar as platelets may model central serotonin neuronal physiology, estrogen's ability to inhibit human platelet serotonin transport may be relevant to consideration of menstrual effects on tricyclic antidepressant response in women, as well as being important as a potential mechanism in the affective variation found in some women across the menstrual cycle.

NR41 Tuesday, May 8, 12 Noon-2:00 P.M.

LIFE EVENTS, DEPRESSION AND IMMUNE FUNCTION

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Summary:

Several reports have recently suggested a possible association between stressful life events, dysphoric mood and immune function. Lymphocyte response to mitogen stimulation has been reported to be suppressed following bereavement and in patients with major depression. To examine the relation between life events, depression and immune function, we studied lymphocyte response to Pokeweed Mitogen (PWM) in 26 drug-free depressed patients, all meeting Research Diagnostic Criteria (RDC) for major depressive disorder. Severity of depression was assessed using the Hamilton Depression Rating Scale (HDRS) and the intensity of stressful life events was evaluated using the Social Readjustment Rating Scale (SRRS) of Holmes and Rahe.

We found no significant correlations between in-vitro lymphocytic responses and either HDRS or SRRS scores. We then divided our patients, on the basis of their SRRS scores, into "high-stress" and "low-stress" groups. There were still no significant associations between stress scores and lymphocyte function. However, when we divided the patients, on the basis of their HDRS scores, between "mildly depressed" and "severely depressed" patients, we found a significant negative association ($X^2 = 6.01$, 1df, $p < .02$) between severity of depression and lymphocytic responses.

These data suggest that depressed mood is more likely to affect immune function than stressful life events, and that lymphocyte mitogenic activity tends to decrease with increasing severity of depression.

NR42 Tuesday, May 8, 12 Noon-2:00 P.M.

IMMUNE RESPONSE IN DEPRESSED AND CUSHINGS PATIENTS

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Summary:

In 9 patients with depression (age 20-61 years) and 5 patients with Cushings disease (age 26-37 years), we compared two measures of immune functioning: 1) natural killer cell activity (NK) and, 2) response to mitogens (concanavalin A, phytohemagglutinin, and pokeweed), with two measures of cortisol function: 1) cortisol levels obtained at the time of immune measures, and 2) dexamethasone suppression test (DST). The immune measures were also compared with the severity of depression as measured by the Hamilton Depression Scale (Ham-D). Each patient was compared with an age, sex and race matched control, who was not depressed or physically ill.

Three depressed patients had markedly decreased NK as compared to their matched controls (at 20:1 effector: target cell ratio, the NK was 7.0 $\pm$ 3.6% killing for depressed patients and 44.3 $\pm$ 17.9% killing for their matched controls). Three depressed patients also had decreased response to mitogens when compared to their controls. Only one patient had both decreased NK and decreased response to mitogens. NK was not related to Ham-D scores, cortisol levels or DST results. However, the three patients with decreased mitogenesis had higher cortisol levels (23.0 $\pm$ 6.7 ug/dl vs 13.5 $\pm$ 4.7 ug/dl), and higher Ham-D scores (30.0 $\pm$ 10.5 vs 18.5 $\pm$ 5.5) than the other 6 depressed patients. DST results were not different.

The Cushings patients had only slightly decreased NK as compared to controls (35.8 $\pm$ 11.5% killing vs 48.4 $\pm$ 11.6% killing at 20:1 ratio). No Cushings patient had a markedly decreased NK that was similar to the levels observed in the three depressed patients. Cushings patients did not have a decreased response to mitogens. However, Cushings patients had a higher WBC (12,100 $\pm$ 5200) and total lymphocyte count (1,975 $\pm$ 380) than did their controls (WBC = 7,620 $\pm$ 3,190; total lymphocyte count = 1,756 $\pm$ 260).

In conclusion, 5 of 9 depressed patients had evidence of immunosuppression. Decreased mitogenesis, but not NK was associated with increased cortisol levels and Ham-D scores. Cushings patients did not demonstrate marked immunosuppression. These data suggest that immunosuppression in depressed patients is not solely dependent on cortisol function.

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THE 0.5, 1.0, AND 2.0 MG. DST: RELATIONSHIP OF DOSE TO DIAGNOSIS

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Summary:

Over the past year, there has been some controversy concerning the dosage of dexamethasone given for the DST in diagnosing HPA overactivity. Though 1 mg. is the standard protocol used, investigators have claimed that 0.5 and 2 mg. have greater meaning in terms of specificity of diagnosis and clinical utility.

We administered 0.5 mg., 1 mg., and 2 mg. of dexamethasone to 26 endogenously depressed outpatients, 24 non-endogenously depressed outpatients, and 16 normal controls. Following this overnight administration, plasma cortisols were drawn at 4 PM the day after the administration of each dose. This procedure was carried out over a 7 to 11 day period.

All depressed patients were evaluated with a Hamilton, Beck, and endogenous symptom profile prior to the DST initiation. Many of the depressed patients were subsequently treated with desipramine (150-300 mg/day) over a 5 week course. At the end of this treatment period, the 1 and 2 mg. DST's were repeated (over a 1 week time course).

The results for each dose of DST for the diagnostic groups are as follows:

+DST (>5 ug/dl)	0.5 mg	1.0 mg	2.0 mg
Endogenous	14/26	12/26	4/26
Non-endogenous	10/24	4/24	2/24
Normal Controls	8/16	3/16	1/16

In addition, we will compare the clinical symptom profile for the endogenous and non-endogenous groups at all doses of dexamethasone. We will further compare whether 0.5 mg., 1 mg., or 2 mg. of dexaemthasone predicted response to desipramine for the depressed group. Finally, we will evaluate the differences of the 1 and 2 mg. dose during depression and following clinical recovery for the depressed group.

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FIBROSITIS RELATED TO MAJOR AFFECTIVE DISORDER

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Summary:

Fibrositis is a form of nonarticular rheumatism characterized by diffuse musculoskeletal pain and increased tenderness at specific "trigger points." The disorder is frequently accompanied by poor sleep, headaches, anergy, anxiety, and irritable bowel syndrome. To investigate the possible relationship between fibrositis and major affective disorder, we evaluated blindly 31 outpatients with fibrositis and 14 outpatients with rheumatoid arthritis for 1) current and lifetime diagnosis of major affective and other disorders, using the NIMH Diagnostic Interview Schedule (DIS), 2) scores on the 21-item Hamilton rating scale (HRS), and 3) family history of major affective disorder among first-degree relatives, employing the family history method. The family study used a control group composed of the first-degree relatives of 15 probands with major depression. The lifetime rate of major affective disorder was significantly higher in the fibrositis patients (71%) than in the rheumatoid arthritis patients (14%; $p<.001$). A current diagnosis of major depression was present in eight (26%) of the fibrositis patients, but in none of the rheumatoid arthritis patients ($p<.04$). In the 22 fibrositis patients with a lifetime diagnosis of major affective disorder, the onset of major affective disorder preceded the onset of fibrositis symptoms in 14 (64%). The fibrositis patients exhibited a mean HRS score of 13.1 (SD 7.0), compared to 7.3 (SD 5.6) in the patients with rheumatoid arthritis ($p<.001$). The morbid risk for major affective disorder among first-degree relatives for the fibrositis patients (17%) was significantly greater than that found for the rheumatoid arthritis patients (5%; $p<.01$), but was comparable to that found for the patients with major depression (18%). These results suggest a relationship between fibrositis and major affective disorder.

NR45 Tuesday, May 8, 12 Noon-2:00 P.M.

AFFECTIVE SYMPTOMS IN BULIMIA: A CONTROLLED STUDY

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Summary:

Affective symptoms are commonly reported in patients with bulimia. However, it is unclear whether these symptoms are due to primary affective disorder, are a form of "atypical" depression, are secondary to the psychological or physiological effects of the eating disorder, or are attributable to an underlying personality disorder. To investigate further the phenomenology of bulimia, we evaluated 28 female outpatient subjects with bulimia ("active bulimics"), and 15 female outpatient subjects with a past history of bulimia, whose disorder had been in remission for at least 6 months ("remitted bulimics"). A comparison group was composed of 14 age-matched female outpatient subjects with major depression ("depressed controls"). An initial interviewer administered the NIMH Diagnostic Interview Schedule and the Atypical Depression Diagnostic Scale of Liebowitz et al. A second interviewer, blind to the subject's primary diagnosis, administered the Diagnostic Interview for Borderlines (DIB). A third interviewer, also blind, evaluated psychiatric illness in the subjects' first-degree relatives by the family history method. The lifetime prevalence of major affective disorder was high in both the active (68%) and remitted (73%) bulimics. In addition, the morbid risk for major affective disorder among first-degree relatives was significantly higher among the active bulimics and remitted bulimics than among depressed controls. However, no significant differences were found between active bulimics, remitted bulimics, and controls on prevalence of atypical depression, nor were any significant differences found among the three groups on prevalence of borderline personality disorder. These results suggest a close relationship between bulimia and major affective disorder, but fail to support an association between bulimia and atypical depression or borderline personality disorder.

NR46 Tuesday, May 8, 12 Noon-2:00 P.M.

BORDERLINE AND CONDUCT DISORDERS IN ADOLESCENCE

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Summary:

INTRODUCTION: Lack of agreement is both historical and contemporary regarding what constitutes the borderline personality, its origin and development, and criteria for differential diagnosis. The current official criteria are reflected in the diagnostic schema; however, lack of preciseness and clarity persists, since many of the discriminating features used in the DSM III diagnosis of borderline personality disorders are also commonly seen in adolescents with conduct disorders. The purpose of this study was to look at the phenomenology, clinical features, developmental history, family history, family interaction patterns, social functioning, and prognostic factors in adolescent patients with both borderline and conduct disorder characteristics.

METHOD: 100 adolescent patients were studied who were consecutively admitted to the Intensive Diagnostic and Treatment Unit of the Children's Psychiatric Institute. This is a JCAH approved 4 month program in which the adolescents were involved in individualized treatment plans that evolved from a multidisciplinary team evaluation, and an evaluation of their family systems. Each had twice weekly individual and group therapy, school, and milieu therapy. Intensive family therapy was undertaken whenever possible. After achieving satisfactory inter-rater reliability, the charts of all patients were examined by members of the team using a structured format to confirm relevant DSM III criteria.

RESULTS: 33 patients satisfied criteria for DSM III Borderline Personality Disorder. Of these 33 patients, 26 also satisfied criteria for Conduct Disorder, Undersocialized, Non-Aggressive. 17 met both the criteria for Conduct Disorder, Undersocialized Aggressive, and Conduct Disorder, Socialized Type. 4 had erratic patterns of eating/sleeping in childhood. 11 had separation problems in childhood. 5 had severe depression. 10 had cognitive deficits on occupation therapy testing. All were experiencing problems with school. 15 had extended family psychopathology, and nuclear families of 31 patients scored over 5 on the global item Beavers Scale for family pathology.

DISCUSSION: Our findings indicate that adolescent patients with Borderline Personality Disorder constitute a heterogeneous group that has many features of the undersocialized conduct disorder group, and come from severely disturbed family systems. Comparison of the phenomenology, clinical features and other characteristics of this group, and the conduct disordered group without borderline features was made.

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THE EFFECTS OF VASOPRESSIN ON THE ORGANIC BRAIN SYNDROME FOLLOWING ECT

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Summary:

Recent research has documented a role in learning and memory for several hypothalamic-hypophyseal hormones. In rats, vasopressin has been reported to reverse an amnesia induced by electroconvulsive treatment (ECT) for a previously learned avoidance response. Results of studies on human subjects suggest that exogenous vasopressin can improve learning and memory in normal and cognitively impaired adults, can reverse traumatic amnesias, and may partially reverse retrograde amnesia following ECT (two reported cases).

This pilot investigation is a double-blind, placebo controlled study designed to assess the effectiveness of exogenous vasopressin (Lypressin-Sandoz) in preventing ECT-induced organic brain syndrome (OBS). Subjects are adult inpatient referrals for ECT treatment of depression, with DSM-III diagnoses of either recurrent affective, bi-polar or schizo-affective disorder.

Subjects are randomly assigned to either the experimental (vasopressin) or a placebo drug group. They receive 16 I/U per day of Lypressin or placebo, intranasally administered in three doses per day, beginning one day after the first ECT, then daily for two weeks. A battery of psychometric measures is administered on six occasions before, during, and after ECT treatments. Measures include the Mini-Mental State Exam (MMS) and the Hamilton Depression Rating Scale (HDRS).

To date, eight (three VP and five placebo) subjects have completed the study. The groups are comparable in terms of age, sex, and diagnosis and both showed a steady decline in depressive symptoms as measured on the HDRS over the course of ECT. Following vasopressin administration, all three vasopressin subjects regained and sustained pre-treatment levels of cognitive functioning over the course of ECT. For this group, MMS scores increased 4.7 points $\pm$ 1.3 ($p \leq .10$). In contrast, the MMS scores of four of the five placebo subjects declined through the course of the six ECT treatments. The placebo group showed a decline of 4.2 points $\pm$ 1.2 ($p \leq .06$) on the MMS. Hamilton Depression Rating Scale scores for the two groups were not significantly different at this time ($t = 1.67$, $p \leq .3$).

Preliminary results suggest that vasopressin may be effective in reducing ECT-induced OBS in patients who have no pre-existing organic brain syndrome. Exogenous vasopressin does not appear to interfere with the effectiveness of ECT in reducing depression. Results for the planned sample of twenty subjects will be presented upon completion of the study.

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CORTISOL RESPONSE TO VASOPRESSIN IN DEPRESSION

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Summary:

A subset of depressed patients is characterized by excessive cortisol secretion. An excess of corticotropin releasing factor (CRF) activity has been hypothesized to explain this phenomenon. Vasopressin is known to potentiate the stimulation of ACTH secretion by CRF. Vasopressin abnormalities have also been implicated in affective disorders. Therefore, we compared the ACTH and cortisol responses to intravenously administered arginine vasopressin (AVP) in depressed and normal groups.

Patients admitted to the VAMC in-patient psychiatric service were screened for the following characteristics: (1) 18-40 years old; (2) no recent alcohol or street drug use reported; (3) no use of psychotropics or other medications; (4) probable clinical diagnosis of major affective disorder - depression; and (5) no history of cardiovascular disease. A diagnosis of depression by DSM III criteria was confirmed by Diagnostic Interview Schedule interviews. Hamilton Depression Scale and Beck Inventory were rated. Two baseline samples were drawn and at 1100 hours, 3 units of arginine vasopressin were given IV. Four cortisol and one ACTH sample were drawn during the next hour. Subsequently, a 1 mg DST with cortisols at 8 AM and 4 PM was performed on the patient group.

Controls showed a mean cortisol increase of 10.75 μg/dl with a standard deviation of 1.34. We defined a "normal" value as lying between the mean $\pm$ three standard deviations (i.e., 6.73 μg/dl to 14.77 μg/dl). Three of the six depressed patients failed to increase cortisol levels after AVP while two patients' responses exceeded the upper limit of the normal response. ACTH changes showed a trend toward correlation with cortisol changes ($r = .698$). Changes in cortisol were not correlated with baseline cortisols ($r = -.265$). No correlation of DST results to vasopressin response was noted.

A subset of depressed patients decrease cortisol levels in response to AVP. The degree of correlation of cortisol response to ACTH changes may reflect a central mechanism. These results provide further evidence for a central abnormality of the hypothalamic-pituitary-adrenal axis in subsets of depressed patients.

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10-HYDROXYNORTRIPTYLINE AND ECG IN THE ELDERLY

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Summary:

We have reported that plasma E-10-hydroxynortriptyline (E-10-OH-NT) concentrations were two-fold greater in elderly compared to young adult depressives treated with equivalent doses of nortriptyline (NT), while plasma NT was not different. Furthermore, plasma E-10-OH-NT/NT ratios varied more than twenty-fold in the elderly. Since E-10-OH-NT is pharmacologically active it may contribute to toxicity. Elderly patients may be sensitive to cardiovascular side effects of tricyclic antidepressants (TCAs) such as NT; although NT is usually well tolerated in the elderly, its cardiovascular side effects vary widely. We have noted acute cardiovascular symptoms in a patient with moderate plasma NT but high plasma E-10-OH-NT. Therefore we have begun to study whether E-10-OH-NT contributes to cardiovascular side effects in the elderly.

Electrocardiograms (ECGs) were obtained before and during treatment with NT in eighteen elderly depressed inpatients. Their median age was 74.5 years and ranged from 61 to 88 years. They were medically stable; two were receiving digitalis. ECGs were obtained during a psychotropic washout period and again after 4 weeks of NT. NT was prescribed at a steady dose of 50-100 mg/day achieved within the first 14 days. Plasma NT and E-10-OH-NT were measured at week 4. ECGs were read blind to plasma concentrations.

Intracardiac conduction changes during treatment were related to plasma E-10-OH-NT. Plasma E-10-OH-NT ranged from 15 to 534 ng/ml, while plasma NT varied from 14 to 270 ng/ml. Six patients had plasma E-10-OH-NT greater than 200 ng/ml; of these, 4 had increases in PR interval and one other developed a right bundle branch block pattern. Among the other 12 patients, 3 had increases in PR ($p=.03$, Fisher exact test). None had increase in QRS. Plasma NT did not differentiate patients with and without conduction changes. Patients with prolonged conduction had somewhat higher E-10-OH-NT/NT ratios (median 2.68 vs. 1.71; NS). Plasma NT was weakly correlated with change in PR ($r_S=.25$); this relationship was strengthened by adding E-10-OH-NT to NT ($r_S=.54$, $p < .10$, two-tailed).

These preliminary data suggest that E-10-OH-NT does contribute to cardiovascular side effects in elderly patients. More research is needed to define the clinical effects of active metabolites of TCAs and related antidepressants, especially in this age group.

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ECT BLUNTS NOREPINEPHRINE REACTIVITY IN DEPRESSION

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Summary:

Alterations of the norepinephrine (NE) neurotransmitter system have been implicated both in the pathophysiology of affective illness and the mechanism of action of antidepressant treatments. Electroconvulsive therapy (ECT) effects on regulation of this system were investigated using an orthostatic challenge procedure prior to and throughout a course of 9-12 bilateral treatments in 4 unmedicated female inpatients with endogenous depression (3 bipolar, 1 unipolar; mean age, 43 yr). On each of several nontreatment mornings over a few wk cardiovascular measures and plasma for NE determination were obtained at baseline and after 5 min of standing. All patients showed good clinical response to ECT. The treatments did not change lying or standing blood pressure or pulse. Lying heart rate was 66 $\pm$ 5 ($\bar{x} \pm$ SEM) beats per min (bpm) before and 64 $\pm$ 8 bpm 1 wk after ECT, with respective values of 83 $\pm$ 12 and 85 $\pm$ 10 bpm on standing. Supine plasma NE decreased nonsignificantly during treatment (1.56 $\pm$ 0.34 vs 1.38 $\pm$ 0.22 pmol/ml). However, NE release on standing was progressively attenuated: pretreatment standing NE was 3.92 $\pm$ 0.66 pmol/ml initially, declining to 3.29 $\pm$ 0.23 after ECT #3 and 2.80 $\pm$ 1.44 following ECT #6, reaching 2.19 $\pm$ 0.50 pmol/ml at completion of treatment ($p < .05$ vs baseline). Thus orthostatic Δ NE, which remained closely correlated with Δ pulse, fell from 2.36 $\pm$ 0.46 to 0.81 $\pm$ 0.39 pmol/ml ($p < .05$) with ECT. Resting plasma MHPG concentrations were not significantly affected by the course of ECT. These results and our earlier finding of lowered daily urinary excretion of NE and its major metabolites during ECT suggest that this treatment is associated with reduced presynaptic NE output without loss of function, indicating increased efficiency of this transmitter system.

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A NEW MARKER FOR NORADENERGIC FUNCTION IN MAN?

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Summary:

Attempts to understand biochemical mechanisms of action of antidepressants currently focus on neurotransmitter alterations, responses to presumed specific agonists in man and animals, or alterations of receptors in brain from the latter. For the noradrenergic system there is substantial evidence that chronic treatment with antidepressants reduces the total turnover of norepinephrine (NE) and alters both pre- and post-synaptic NE receptors. Reduced number or sensitivity of alpha-2 and beta receptors suggests that treatments increase intra-synaptic NE. Reduced turnover of NE can also be interpreted in this way. Decreases of both receptors and turnover, however, do not provide information on resultant function. For instance, physiologic parameters such as cardiovascular function, known to be partly controlled by NE, show variable changes not easily explicable on the basis of common alterations in central nervous system (CNS) NE.

Melatonin (M) output from the pineal gland may provide an index of beta NE function since secretion of this hormone, at least in the rat, is dependent on a NE pathway under CNS control. Since most M is metabolized to hydroxy-melatonin (OH-M) prior to renal excretion, the amount of OH-M per 24 hour urine collection provides an integrated measure of total daily M output. In patients treated with desipramine (DMI), a tricyclic antidepressant specific for NE reuptake inhibition, we have found decreased NE turnover as evidenced by both CSF and urine measures. In five of these same patients we were able to study OH-M excretion, which increased by 64% (9.37$\pm$ 2.10 to 15.40$\pm$ 2.13 mcg./24 hr., $p<.01$) after DMI. Moreover, pre-treatment OH-M output was correlated with the total turnover of NE in these patients ($r=.83$, $p<.05$). Thus at least one antidepressant, DMI, increases mean central NE function as indexed by OH-M output despite reductions in turnover. If this proves true for other classes of antidepressants, it will provide the most direct evidence so far available in man that an increase in NE function is indeed involved in the action of antidepressants.

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IMIPRAMINE BINDING IN SUBTYPES OF DEPRESSION

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Summary:

Some patients with primary major depression (PMD) exhibit decreased binding of ^{3}H-imipramine to platelet membranes. However, there has been no attempt to determine if this decreased binding capacity is associated with particular subtypes of PMD. We measured the binding of ^{3}H-imipramine to platelet membranes in 45 patients with unipolar (UP) or bipolar (BP) PMD (Research Diagnostic Criteria) and in 20 healthy controls (CON). UP patients were segregated by family history into the familial subtypes described by Winokur: familial pure depression (FPDD), sporadic depression (SDD) and depression spectrum (DSD). Subjects had not received tricyclic antidepressants for 3 weeks prior to testing. Platelets were obtained between 0700 and 0900 hrs. and were incubated with increasing concentrations of ^{3}H-imipramine (0.5 - 10nM) and 100 µM unlabeled desipramine at 0°C for 60 min. Maximal concentration of binding sites (Bmax) and dissociation constants (Kd) were calculated from Scatchard analyses. Mean Bmax (fm/mg protein) for PMD (1069 ± 316) was significantly lower ($p < 0.006$) than for CON (1238 ± 201). Among subjects with PMD, only FPDD and BP subjects had significantly decreased Bmax values (ANOVA $p < 0.001$).

	CON	DSD	SDD	FPPD	BP
n	20	15	13	11	6
Bmax (Mean ± SD)	1238 ± 201[a]	1236 ± 241[a]	1188 ± 325[a]	870 ± 241[b]	754 ± 149[b]

(values with same letter are not significantly different p=.05)

These differences could not be explained by differences in age, sex, presence of psychotic features, Hamilton rating score or medications among the groups. Kd values were not significantly different among the groups. Our findings indicate that decreased Bmax values in patients with PMD are due to substantially lower values in certain subtypes. This association of a biological finding with distinct clinically-defined subtypes of depression may lead to a classification of affective disorders useful in further research.

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MELATONIN/CORTISOL RATIO: A BIOLOGICAL MARKER?

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Summary:

Recently a dysfunction of the pineal-hypothalamic-pituitary axis in melancholic [dexamethasone nonsuppressors (DST+)] patients has been suggested.

In this study we report on the relationship between melatonin (M), cortisol (C), and the DST in fourty-three (26 females, 17 males) newly admitted psychiatric inpatients. Patients were kept medication free for at least one week prior to and throughout the study. Twenty-five of the patients qualified for the diagnosis of primary major depressive disorder with melancholia (MDD), ten for schizophrenia (S), and eight for personality disorder with superimposed depression (PD/SD) by Research Diagnostic Criteria. Patients were under controlled dark/light conditions for the three nights of the study (lights on between 0600 and 2130 hrs). Blood samples for M and C were drawn at 0200, 0800, 1600 and 2300 hrs on 2 consecutive days. Dexamethasone (1 mg, p.o.) was administered at 2305 of Day 1. A cortisol concentration > 138 nmol/L in any of the Day 2 samples was considered as non-suppression.

Thirteen of the twenty-five MDD patients were DST+; all other patients had a normal DST. All patients showed a marked melatonin circadian secretory rhythm with very low (mostly undetectable) levels during the day.

There was no difference in the 0200 M levels, in 0200 M/C ratios, or in the entire M profile between MDD/DST+, MDD/DST-, and the PD/SD groups. When all the depressives together were compared to the schizophrenic group, a difference was found in 0200 M levels and in the 0200 M/C ratios on both days of the study, with melatonin and ratios being significantly lower in the depressed patients. Dexamethasone did not have a significant influence on any of the Day 2 melatonin samples.

The independence of the pineal function in depression and the possible role of melatonin as a trait marker vis-a-vis cortisol as a state marker will be discussed.

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SERUM MELATONIN IN MELANCHOLIA

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Summary:

Serum melatonin concentration in humans reflects pineal beta-adrenergic activity, and appears to relate to circadian sleep and hormonal rhythms of interest in affective disorders. Recent development of sensitive and specific RIAs for melatonin in human serum now permit investigation of this biological marker in depression. Methods: 24 unmedicated, hospitalized patients with DSM III major depressive disorder, and 10 healthy controls were studied. One psychotic manic patient was also studied. Serum was obtained at 0900 and 2300 hours. Lights were off for one hour prior to nighttime venipuncture. Melatonin was determined by RIA. Results: Serum melatonin concentration was significantly decreased in the 24 melancholic patients at 2300 hours ($\bar{x}$ = 34.1 $\pm$SD = 20.9), compared to normals ($\bar{x}$ = 52.6, $\pm$SD = 23.4, $p < 0.05$). There was a trend for 8 nonmelancholic major depressives to have higher melatonin levels at 2300 hours ($\bar{x}$ = 52.4 $\pm$SD = 23.8, $p = 0.08$) compared to melancholic patients but not different from normals. 0900 values did not show significant differences between depressed patients and normals. One manic patient showed an unusually high 0900 value of 141.5, pretreatment, which reverted to a typical 0900 value of 21.3 after 4 weeks of lithium treatment. Discussion: Preliminary findings of altered melatonin secretion in endogenous major depression support the possibility of altered activity of beta-adrenergic or related neurotransmitter systems. Further investigation will be necessary to confirm this finding and to investigate its relationships to variables such as clinical state, other proposed biological markers, and treatment response, and also to determine specificity to affective diagnosis.

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SEROTONIN BINDING SITES ON HUMAN PLATELETS

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Summary:

Reports of altered serotonergic function in the central nervous systems of patients with depression, autism, mental retardation, and suicidal behavior have prompted interest in assessment of serotonergic receptors in these disorders. In our laboratory, we have found a decrease in the density of the serotonin-two ($5\text{-}HT_2$) receptor in postmortem brain samples from suicide victims versus controls. Somatic antidepressant treatments including tricyclic antidepressants and ECT alter the density of $5\text{-}HT_2$ binding sites in mammalian frontal cortex.

In recent years, the blood platelet has been increasingly utilized as a model for the serotonergic neuron. Since central receptor function cannot be measured directly in living patients, we decided to characterize serotonin-related binding sites on the intact human platelet. A high affinity, saturable ^3H-spiroperidol binding site was demonstrated for the first time on the intact human platelet with properties similar to the $5\text{-}HT_2$ receptor in human brain. Scatchard analysis of binding data from five healthy male subjects yielded an affinity constant (K_D) of 2.7 ± 0.3 nM for the platelet site, with a maximal number of binding sites (B_{max}) of 1.4 ± 0.2 pmoles/10^8 platelets. Within these five subjects, inter-individual variance was less than that described for other platelet measures such as MAO activity. Binding was preferentially displaced by serotonin antagonists such as ketanserin and cinanserin (IC_{50s} 87nM and 77·nM), in contrast to serotonin uptake inhibitors and dopamine antagonists ($IC_{50s} < 10uM$). The IC_{50s} of these agents for ^3H-spiroperidol binding to intact platelets showed a strong, statistically significant positive correlation with the IC_{50s} for binding to human frontal cortex, with $r=0.95$, $p < 0.001$. A single population of ^3H-serotinin binding sites was also located on the intact human platelet, which appeared to represent the serotonin uptake site. The K_D of this site was 42 ± 18 nM. No ^3H-serotonin binding site with features of the $5\text{-}HT_1$ receptor in brain was located on the human platelet.

The results described above suggest that the $5\text{-}HT_2$ site on the intact human platelet could be used as a model to explore potential alterations in central $5\text{-}HT_2$ receptor function in a number of psychiatric and neurologic illnesses. Preliminary data will be presented from our current study of platelet $5\text{-}HT_2$ receptor binding in depressed patients and of the interaction of this receptor with typical and atypical antidepressants as well as with other psychoactive medications affecting serotonin metabolism such as fenfluramine.

NR56 Tuesday, May 8, 12 Noon-2:00 P.M.

EFFECTS OF ALPHA-2 ADRENOCEPTOR BLOCKADE IN DEPRESSION

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Summary:

Abnormalities in central neurotransmitter receptor function may be involved in the pathogenesis of depression. Yohimbine increases brain norepinephrine turnover by blocking alpha-2 adrenoceptors. Noradrenergic function in depression can be assessed by measuring the behavioral, physiologic, and biochemical response to yohimbine in depressed patients compared with other patients and healthy controls. Methods: Using DSM III criteria, 45 patients with major depression (20 nonmelancholics, 14 nonpsychotic melancholics, and 11 psychotic melancholics), 39 patients with agoraphobia with panic attacks, and 20 healthy subjects were selected after giving voluntary informed consent. All subjects were free of psychotropic medication for at least 3 weeks prior to the study. On 2 different days, after an overnight fast, each subject received yohimbine 20 mgm by mouth or a matching placebo. Subjective ratings, blood pressure (BP) and pulse, and plasma free 3 methoxy-4 hydroxyphenelethylene glycol (MHPG) were obtained before and for 4 hours after the dose. Results: In the depressed patients, yohimbine produced an increase in nervous, anxious, and energetic, and a decrease in calm and drowsy ratings. Ratings of 10 of the 12 autonomic symptom items increased. There were significant peak increases in systolic and diastolic BP and MHPG. Compared to healthy subjects, depressed patients had less drowsiness and increased autonomic symptoms on 6 of the 12 scales. Depressives tended to have a larger systolic BP increase than controls, but MHPG changes were similar. There were not marked differences between depressive subtypes except that melancholic patients had higher baseline MHPG levels. Compared to the total anxiety patient group, depressives had smaller increases in nervous, anxious, sad, depressed, and drowsy. Changes in autonomic symptoms, BP, and MHPG were similar. Anxiety patients with frequent panic attacks were identified to be highly sensitive to yohimbine, with greater increases in behavioral and autonomic symptoms, BP, and MHPG than other anxiety patients, depressives, and controls. Conclusion: The MHPG response to yohimbine differed little between depressed patients and controls, but depressives reported greater autonomic arousal than normals. The depressed patients developed less anxiety-like symptoms than anxiety disorder patients, and a smaller MHPG response than anxiety patients with frequent panic attacks.

NR57 Tuesday, May 8, 12 Noon-2:00 P.M.

FACIAL ELECTROMYOGRAPHIC LEVELS PREDICT OUTCOME IN DEPRESSION

John F. Greden, M.D., Director, Clinical Studies Unit, University of Michigan Medical Center, Ann Arbor, MI 48109, H. Laurence Price, M.S. (I), Nancy Genero, M.A. (I), Michael Feinberg, M.D., Simon Levine, Ph.D. (I), Ann Arbor, MI

Summary:

Facial muscle contractions reflect psychomotor function in depressed patients. In the 1970's, Schwartz et al reported that electromyographic (EMG) measures of facial muscles during states of affective imagery diagnostically differentiated between depressives and normals. These results were replicated in four subsequent studies by other investigators.

Schwartz et al (1978) and Carney et al (1981) reported also that higher pre-treatment EMG activity predicted better clinical outcome in depressed patients. These innovative pilot assessments were limited however, by methodological shortcomings (no drug washouts, heterogeneous diagnostic subgroups, absence of treatment monitoring, etc.).

We studied whether pre-treatment facial EMG levels predicted better treatment response while controlling for major methodological variables. We measured EMG activity of corrugator and zygomatic muscles during resting and three imagery states in 29 right-handed, non-delusional drug-free depressed women hospitalized in the Clinical Studies Unit. Clinicians blind to EMG results diagnosed each patient using SADS and RDC criteria as having major depressive disorder, endogenous subtype. Treatment adequacy was monitored with tricyclic plasma levels. Good responders were operationally defined as those with at least a 50 percent decrease in HRSD scores and a final HRSD score of less than 10. Outcome was validated with self-ratings and dexamethasone suppression test results.

"Good responders" had significantly higher pre-treatment EMG zygomatic values than poor responders ($p < .02$). Their EMG profiles differed significantly (parallelism of profiles, $p < .04$). A discriminant function (DF) index combining EMG levels with several clinical variables predicted good outcome with a sensitivity of 94%, specificity of 100% and a predictive value of 100%. The predictive value for poor outcome was only 86%. These data support prior findings that pre-treatment facial EMG values may predict treatment outcome in endogenous depressives treated with antidepressants. They also validate numerous historical reports that psychomotor agitation and retardation are among the most important clinical predictors of treatment outcome.

NR58 Tuesday, May 8, 12 Noon-2:00 P.M.

POOR RESPONSE TO PSYCHOTHERAPIES IN MELANCHOLIA

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Summary:

It is unclear if the newer, short-term psychotherapies can be effective primary treatments for more severe and pervasive depressive syndromes. This report addresses this issue, by comparing the efficacy of psychosocial treatments (PSY) versus that of amitriptyline (AMI) in 26 women with DSM-III melancholia. Patients were selected from a larger sample of 135 female major depressives who were treated in a recently completed, randomized, controlled outpatient trial.

Patients received up to 12 weeks of treatment with either AMI (n=9, mean daily dose=225 mg) or one of two forms of psychosocial therapy (social skills training, n=8, or interpersonally-oriented psychotherapy, n=9). Sixteen of 17 PSY patients concomitantly received placebo; amitriptyline and inert placebo were administered "double blind". Independent clinical assessments were completed at baseline and following six and twelve weeks of treatment. As previous research had shown no major differences in efficacy, the two forms of psychosocial treatment were grouped together for statistical comparisons versus AMI. It was predicted that AMI would be superior to PSY in this melancholic subsample. Response was defined as $\geq$ 50% reduction of Hamilton scores.

Response rate to AMI was double that seen in patients receiving PSY (78% versus 38%, χ^2=2.72, p<.05). By contrast, 73% of nonmelancholic patients in the total sample had responded to psychosocial treatment (χ^2=5.88, p<.01). Nonresponse to PSY in melancholic patients principally was reflected by a significantly higher rate of premature termination when compared to AMI (41% versus 0%; χ^2=3.20, p<.05). Melancholic patients who completed 12 weeks of treatment with PSY showed significantly greater improvements in social adjustment (p<.05) and decreased levels of neuroticism (p<.01) than AMI patients. However, when the effect of differential attrition was controlled by use of end-point scores, these differences vanished.

Overall, results indicate that short-term psychosocial treatments, such as social skills training and interpersonally-oriented psychotherapy, are less effective and less well-tolerated than pharmacotherapy with melancholic outpatients. Such treatments may be relatively indicated for nonmelancholic major and minor depressive disorders. They may also prove useful in combination with pharmacotherapy for more severely depressed patients. Poor response to psychosocial treatment in melancholia may be related to the presence of an autonomous, biological dysfunction, as evidenced by neuroendocrine test abnormalities and EEG sleep disturbances. Implications for future research are discussed.

NR59 Tuesday, May 8, 12 Noon-2:00 P.M.

EARLY VERSUS LATE PARTIAL SLEEP DEPRIVATION

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Summary:

Some studies show that the timing of various circadian rhythms and REM sleep appears to be shifted to an abnormally early time in depression. In patients with phase-advanced circadian rhythms, both the phase-advance treatment and partial sleep deprivation in the second half of the night shifts sleep period earlier, restoring a more normal relationship between sleep and the other circadian rhythms. If the timing of sleep and not the duration is the critical factor in the sleep deprivation response, then partial sleep deprivation in the first half of the night should not have therapeutic effects.

In this study we have examined the relative efficacy of partial sleep deprivation (PSD) in the first half of the night (E = early) and PSD in the second half of the night (L = late) in a randomized crossover design. All depressed patients underwent baseline sleep, temperature, activity, (24 hour) U.F.C., TRH stimulated TSH response and 24 hour urinary collections for norepinephrine, serotonin and their metabolites in order to investigate the relationship between the sleep depression response and the current biochemical and neuroendocrine hypotheses of depression.

Of 18 drug-free depressed patients (9 UP, 9 BP), 11 responded to PSD. All 11 improved on the PSD-L condition. None responded when kept awake in the first half of the night. Results of this study support the hypothesis that the internal phase relationship between sleep and other circadian rhythms is critical to the antidepressant response of PSD. In addition, the response to PSD was not restricted to the first night. Improvement was sustained through a second night of PSD and a night of recovery sleep.

NR60 Tuesday, May 8, 12 Noon-2:00 P.M.

CHRONIC DEPRESSION AND ITS TREATMENT

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Summary:

Antidepressants are effective in the treatment of acute depressive episodes. Their efficacy for more chronic forms of depression, however, has not been clearly established. Therefore, the evaluation of the efficacy of established and novel antidepressants for the treatment of chronic depression is of clinical interest. This study reports on the efficacy of placebo (P), amitriptyline (AMI)and bupropion (BUP), a novel unicyclic antidepressant, for acute and chronic depression.

METHOD: A total of 727 patients suffering from nonpsychotic depressive disorder (DSM-II and DSM-III criteria, depending on time of enrollment) were entered in 18 multicenter, double blind, randomly assigned, placebo controlled studies. Evaluated was the efficacy of AMI (dose average 150mg) and BUP (dose average 450mg), for the treatment of chronic depression (lasting a year or longer prior to enrollment) in contrast to acute depression. Parameters of efficacy included the Hamilton Depression Scale (Ham-D) and the Clinical Global Improvement Scale (CGI). Analysis of variance was used to determine statistically significant effects.

RESULTS: As expected acute depression showed marked improvement from baseline on both AMI (baseline Ham-D=28, week 4 Ham-D=12) and BUP (baseline Ham-D=28, week 4 Ham-D=14), but significantly less on P (baseline Ham-D=31, week 4 Ham-D=20); $p \leq 0.0001$ for BUP over P after week 4, but no difference between AMI and BUP. Chronic depression responded to both BUP and AMI, (BUP baseline Ham-D=29, week 4 Ham-D=14, AMI baseline Ham-D=27, week 4 Ham-D=16) with a statistically significant trend in favor of BUP ($p \leq .09$). Chronic depression responded less to P (baseline Ham-D=31, week 4 Ham-D=23) $p \leq 0.05$ for BUP vs. P.

CONCLUSION: AMI and BUP are effective in the treatment of acute depression. In the treatment of chronic depression, the new compound BUP has a slight edge. The weak dopaminergic activity of BUP in comparison to the serotonergic and noradrenergic activity of AMI will be discussed in light of these findings. BUP's mode of action and its efficacy in chronic depression may point to an affective disorder biochemically distinct from the more acute forms.

NR61 Tuesday, May 8, 12 Noon-2:00 P.M.

LITHIUM-INDUCED HYPOTHYROIDISM

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Summary:

It has been common practice to follow peripheral thyroid hormones or thyroid stimulating hormone (TSH) as indicators of failing thyroid function in patients receiving lithium. Although it is not currently being used routinely, it may be that the thyrotropin releasing hormone (TRH) test could be a more sensitive and early indicator of impaired thyroid function in these patients.

To test this hypothesis the TSH response to TRH (500 mg I.V.) in ten patients (seven males, three females ranging in age from 17 to 45 was measured. Prior to treatment, all patients exhibited normal TSH responses to TRH and had normal baseline thyroid laboratory values including TSH, T_4 (thyroxine), T_3RU (T_3 resin uptake), and T_3RIA (triiodothyronine). Serum lithium levels ranged from 0.6 to 1.0 mEq/l, in patients treated for eight weeks prior to re-testing with TRH infusion.

All patients had normal baseline thyroid values on re-testing, and had no clinical symptoms suggesting impaired thyroid function. Two of these eight patients had abnormally augmented TSH responses to TRH (23.9 and 21.0 uIU/ml after three and five weeks, respectively, of treatment). Both of these patients had slight elevations of TSH levels over baseline values but which were within normal limits. One of the patients had mild symptoms of anergia, dysphoria, and irritability which improved on discontinuation of lithium. Mean Δ TSH was increased significantly from 12.4 uIU/ml $\pm$ 1.5 to 17.5 uIU/ml $\pm$ 2.0.

It has been shown that depression and hypothyroidism share several clinical features including anergy, appetite disturbance, weight change, and constipation. Up to eight percent of inpatients and 13.5% of outpatients (1) with depression have been shown to have some degree of hypothyroidism as measured by TRH testing. The current study extended the use of the TRH test to examine possible changes in thyroid function in 10 euthyroid patients after receiving lithium for 8 weeks.

These findings suggest that lithium has antithyroid effects in all patients. Symptoms of depression emerging while a patient is receiving lithium could be an early manifestation of lithium-induced subclinical hypothyroidism rather than depression.

1. Sternbach,HA; Gold,MS;Pottash,ALC; Extein,I: Thyroid failure and protirelin (thyrotropin-releasing hormone) test abnormalities in depressed outpatients. JAMA 249:1618-1620, 1983.

NR62 Tuesday, May 8, 12 Noon-2:00 P.M.

3-METHOXY-4-HYDROXYPHENYL-GLYCOL (MHPG) IN DEPRESSION

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Summary:

MHPG is a major common metabolite of both the catecholamine neurotransmitters norepinephrine (NE) and epinephrine (E). In many studies examining the involvement of catecholamine in depression, MHPG has been measured as an index of catecholamine activity in cerebrospinal fluid (CSF) or 24-hour collections of urine. This report from the NIMH Collaborative Program on the Psychobiology of Depression-Biological Study is on the relationship of plasma MHPG to both CSF and Urinary MHPG in depression and healthy controls. We previously reported (Archives of Gen. Psych. 40: 999-1010, 1983) that in general there exists a hyperadrenergic state in depression as compared to normal healthy controls. The data to be reported will examine the ability of plasma MHPG to measure this state. A number of reports in addition to our own data show that urinary MHPG can be used as a predictor for therapeutic outcome (Psychological Medicine 12: 37-43, 1982). The use of plasma MHPG as an index of adrenergic function may be of greater value given the inherent problems in sampling either CSF or urine. Data will be presented on the usefulness of plasma MHPG as a predictor for therapeutic outcome in depression.

NR63 Tuesday, May 8, 12 Noon-2:00 P.M.

PLATELET MAO ACTIVITY IN SUBTYPES OF DEPRESSIONS

Jacqueline Samson, Ph.D. (I), Massachusetts Mental Health Center, 74 Fenwood Road, Boston, MA 02115, Jon Gudeman, M.D., Patricia Kizuka, B.S. (I), Alan Schatzberg, M.D., Jonathan O. Cole, M.D., Joseph Schildkraut, M.D., Boston, MA

Summary:

There are many apparent discrepancies in the extensive literature on platelet monoamine oxidase (MAO) activity in subtypes of depressive disorders, which may be related in part to differences in severity as well as to differences in the diagnostic systems used to classify depressions. To address these issues, we systematically examined platelet MAO activity, clinical symptoms and symptom severity across a variety of diagnostic categories based on the Research Diagnostic Criteria (RDC).

Platelet MAO activity was examined in a sample of 77 patients (40 males and 37 females) with definite major depressive disorders and 28 controls (14 males and 14 females) whose ages ranged from 18-68 years. The 24-item Hamilton Rating Scale for Depression was used to assess symptom severity.

Significantly higher mean platelet MAO activity was observed in unipolar depressions meeting criteria for definite endogenous depressive syndrome than in other unipolar depressions ($t=3.85$, $p < .001$). Moreover, unipolar endogenous depressions showed significantly higher platelet MAO activity than bipolar endogenous depressions ($t=4.17$, $p < .001$).

The presence of a definite endogenous syndrome was associated with greater overall symptom severity in both unipolar ($t=2.46$, $p < .05$) and bipolar ($t=2.84$, $p < .01$) depressions. These results suggested that platelet MAO activity is related to the severity of symptoms in depressive disorders, and that symptom severity is associated with high MAO activity in unipolar depressive disorders and with low MAO activity in bipolar depressive disorders.

An analysis of variance, which controlled for the simultaneous effects of age, sex, anxiety and severity showed a significant main effect ($F=13.4$, $p < .001$) for the presence of a definite endogenous depressive syndrome and a significant interaction effect ($F=9.2$, $p < .01$) between the presence of an endogenous syndrome and polarity (unipolar vs. bipolar). These recent findings will be discussed in relation to the conflicting literature on platelet MAO activity in the depressive disorders.

NR64 Tuesday, May 8, 12 Noon-2:00 P.M.

DEPRESSIONS AND RECEPTOR-ADENYLATE CYCLASE LINKAGE

John J. Mooney, M.D. (I), Massachusetts Mental Health Center, 74 Fenwood Road, Boston, MA 02115, Alan F. Schatzberg, M.D., Jonathan O. Cole, M.D., Patricia P. Kizuka, B.S. (I), Joseph J. Schildkraut, M.D., Boston, MA

Summary:

Recent studies (ACNP, 1983) reported subsensitivity of prostaglandin stimulation of adenylate cyclase, decreased potency of α-adrenergic suppression of prostaglandin-stimulated adenylate cyclase and an increased density of high affinity α_2-adrenergic receptors in platelets from depressed patients (Siever, et al.; Smith, et al.; U'Pritchard, et al.). These data suggest a deficiency in receptor-adenylate cyclase coupling which may involve the guanine nucleotide regulatory (N) proteins which link prostaglandin and α_2-adrenergic receptors to adenylate cyclase. Moreover, Menkes, et al. (Science, 1983) have found that the activity of the stimulatory N protein in rat brain was enhanced by several chronically-administered antidepressant therapies. In a currently ongoing study we have observed enhanced platelet adenylate cyclase responses to prostaglandin stimulation, enhanced epinephrine suppression of prostaglandin-stimulated adenylate cyclase, and an apparent increase in platelet stimulatory N protein activity to sodium fluoride (NaF) after treatment with alprazolam in patients who showed favorable antidepressant responses but not in those who failed to respond.

Data are presently available on 11 depressed patients, 6 of whom had favorable antidepressant responses to alprazolam. After 8 days of treatment, significantly enhanced prostaglandin-stimulated adenylate cyclase ($p < .01$), greater suppression of prostaglandin-stimulated adenylate cyclase by epinephrine ($p < .02$), and enhanced responsiveness of the stimulatory N protein to NaF ($p < .04$) occurred in the platelets of responders but not in nonresponders. No meaningful changes were observed in the mean density (Bmax) or dissociation constant (K_D) of the platelet high-affinity α_2-adrenergic receptors. The present findings, taken in conjunction with findings from other recent studies, suggest that an enhanced linkage between certain hormone receptors and adenylate cyclase through the N proteins may help explain the antidepressant effects of alprazolam and possibly other forms of antidepressant treatment.

NR65 Tuesday, May 8, 12 Noon-2:00 P.M.

INTERACTION SEQUENCES: ADOLESCENTS AND PARENTS

Stuart T. Hauser, M.D., Massachusetts Mental Health Center, 74 Fenwood Road, Boston, MA 02115, John Houlihan, M.A. (1), Sally Powers, Ed.D. (1), Alan Jacobson, M.D., Gil Noam, Dipl. Psych. (1), Bedonna Weiss, M.A. (1), Donna Follansbee, Ph.D. (1), Boston, MA

Summary:

We report analyses of family interaction patterns, focussing on clinically-relevant processes occurring between adolescents and parents. To systematically assess interaction processes (e.g., reciprocity), we apply analyses to chains of speeches rather than frequency analyses of separate speeches. Our general hypothesis was that there would be more undermining and cross-purpose sequences in psychiatric families, in contrast to positive recripocal (e.g. mutual problem solving) sequences in non-patient families.

Sixty 2-parent families with an early adolescent were studied: a psychiatrically hospitalized group (adolescent adjustment and conduct disorder; n=25) and non-patient high school students (n=35). Students were matched with patients for age, sex, social class. Family discussions generated through a revealed-differences procedure were taped and coded, using the Constraining and Enabling Coding System (CECS), a family coding technique with sensitivity to adolescent developmental impairments, and favorable reliabilities. All speeches were scored for enabling (e.g. accepting), and constraining (e.g., distracting) properties. Sequential analyses were applied to the scored adolescent-parent and parent-parent pairs. Two way ANOVAs revealed multiple significant differences between patient and non-patient families, present for both sexes. Adolescent patients were more often at odds with either parent, and less likely to collaborate following parent speeches. For example, patient families had significantly higher cross-purposes ($F=4.2$; $p<.05$) and asynchrony scores. Patient families also had lower positive reciprocity, when adolescents followed parents ($F=4.6$; $p<.04$). This consistency was not found for pairs where parents spoke after adolescents. Here, patient families had significantly lower mutual distracting and mutual overall constraining scores. Findings indicate that psychiatric patients are not simply responding to pathological parent communications. Rather, patients oppose parent efforts towards resolving differences within the family, while parents continue to offer assistance. Additional results indicate that parents of patients are more mutually enabling to one another.

A study of these families using frequency analyses of these codes did not discriminate between patient and normal families, thus underscoring the greater sensitivity of process indices. Sequence analysis offers a tool for clarifying basic theoretical questions as direction of influence, and concepts regarding pathological parenting, reactive parenting, or negative reactivity of selected family members. Our ongoing longitudinal analyses of these families explore associations between family process change and variations in psychiatric outcome.

NR66 Tuesday, May 8, 12 Noon-2:00 P.M.

PRIMARY VERSUS SECONDARY DEPRESSION

Daljit S. Mac, M.D., University of Kansas Medical Center, 39th and Rainbow Boulevard, Kansas City, KS 66103, Sieglinde C. Othmer, Ph.D. (I), Ekkehard Othmer, M.D., Sheldon Preskorn, M.D., Rajiv Kumar, M.D., Kansas City, KS

Summary:

In the primary vs. secondary dichotomy, depression without other psychiatric disorders is classified as primary, while depression with other non-affective psychiatric disorders is called secondary depression. In this study we tested the clinical usefulness of the concept of primary and secondary depression with respect to treatment response. 40 inpatients who were 18 years or older meeting the DSM-III criteria for major depression were enrolled. All patients were subdivided into a primary or secondary depression group on the basis of the Psychiatric Diagnostic Interview (PDI). The PDI is a structured interview based upon a descriptive syndromatic model of psychiatric diagnosis. Primary depression was defined as depression being the only psychiatric diagnosis established with the PDI. Secondary depression group patients were positive for depression and one or more additional non-affective psychiatric disorder. Patients in both diagnostic groups were randomly assigned to one of two treatment modalities, either amitriptyline (AMI) or bupropion(BUP) in a double blind fashion. After one drug free week,patients were given ascending doses of the drug for 2 weeks. For the following 4 weeks the dosage was held constant to establish efficacy at a given steady-state plasma level. Plasma levels were drawn at weekly intervals. Psychiatric measures taken at baseline and weekly intervals were the Hamilton Depression Scales,the Clinical Gloval Impression Scale, the Zung Self Rating Depression and the SCL-90. Patients did not differ in their demographic variables between the two groups. The baseline Hamilton depression scores (HDS) for patients with primary and secondary depression were the same 31±5 ($\bar{X}$±S.D.). Both groups improved at the same rate. After 28 days HDS were 7±5 for primary and 8±4 for secondary depression. Primary and secondary depressives were further compared with respect to their response to both amitriptyline and bupropion. Neither diagnosis nor pharmacological agents produced a significant difference in treatment response at any of the assessment points.

	N	Sex M/F	Age (yrs) $\bar{X}$ ± S.D.	Pt's treated with Ami/Bup	Dose Range Ami (mg)	Dose Range Bup (mg)
Primary Depression	19	5/14	43 ± 14	8/7	144 ± 18	563 ± 133
Secondary Depression	18	5/13	35 ± 13	8/7	147 ± 39	557 ± 167

At this point we conclude that the subclassification of depression on the basis of psychiatric history is plausible and attractive, but lacks the merit of clinical usefulness with respect to treatment outcome.

Oral/Slide Papers

NR67 Wednesday, May 9, 1984, 10:15 A.M.

ADVANCES IN PSYCHOTHERAPY RESEARCH

John P. Docherty, M.D., NIMH, Parklawn Building, Room 10C-05, 5600 Fishers Lane, Rockville, MD 20857

Summary:

Recent carefully conducted meta analytic reviews of the psychotherapy research literature strongly support the efficacy of psychotherapy as a generic form of treatment. Recent advances in the methodology and technology of psychotherapy outcome and process research have provided the field with effective means for addressing the important question of the specificity of psychotherapeutic treatments, that is, with what defined range of disorder are specific treatments particularly effective.

In the area of outcome research, these advances have been centered upon the development of ways to standardize the psychotherapeutic treatment. This work represents a major advance in the history of psychotherapy research. Current procedures for such standardization include: (1) quantitative criteria and defined procedures for the selection of therapists, (2) therapy manuals, (3) audiovisual therapy libraries, (4) carefully defined didactic and supervisory training programs, (5) quantitative criteria for the assessment of therapists' competency, (6) the use of independent expert judges to assess therapists' competency, (7) standardized therapy monitoring procedures, and (8) content analytic techniques for establishing the uniqueness of a therapy and the fidelity with which it is practiced.

Process research has been advanced substantially in at least four areas. First, studies of the therapeutic alliance have benefited from the development of a coordinated series of measurements applicable to videotaped material for the measurement by independent observers, patients, and therapists of the therapeutic alliance. This work has demonstrated the relationship between the strength of the therapeutic alliance and outcome of psychotherapy. Procedures have further been developed for the testing of the therapeutic alliance across therapy modalities. A second major area of activity has been the elaboration of a "key events" strategy for the analysis of critical change elements in psychotherapy. This refers to procedures for the standardized identification of "critical moments" in the course of a psychotherapy and the ramifications of such moments. Third is the emerging area of the development of objective quantative measures of transference, and fourth is the use of increasingly sophisticated techniques for sequence analysis to study the process of therapeutic change. Specific examples of the application of these new methods and their implications for future directions of psychotherapy research will be presented.

NR68 Wednesday, May 9, 10:30 A.M.

FAMILY ENVIRONMENT LOWERS REHOSPITALIZATION RATE

David Spiegel, M.D., Stanford University School of Medicine, Department of Psychiatry and Behavioral Sciences, Stanford, CA 94305, Terry Wissler, Psy.D. (I), Stanford, CA

Summary:

The Family Environment Scale (FES) of Moos and Moos was administered to 108 psychiatric inpatients and their families at discharge from hospitalization. Patients were diagnosed according to research diagnostic criteria: 32% were schizophrenic; 23% had unipolar depressive disorders; 17%, manic or bipolar disorders; 13%, alcohol and drug abuse; and 14%, other disorders. Patients were evaluated at 3-month and 1-year follow-up after discharge for rehospitalization history, self-rated adjustment using the Vets Adjustment Scale, and a family rating of the patient with the Personal and Role Skills Scale. Data were analyzed using stepwise multiple regression with rehospitalization and adjustment data as dependent variables. Supportive elements of family environment were found to be more potent predictors of lower rehospitalization rates than were negative elements in predicting more rehospitalization. In particular, the Expressiveness subscale of the FES predicted significantly fewer days of rehospitalization at 3 months (beta = -.39) and 1 year (beta = -.33). This measure of shared problem-solving is different from the high expressed emotion construct of Brown, Birley & Wing, which largely reflects criticism of the patient family member. Indeed, among the 36 schizophrenics in the sample, high expressiveness was a strong predictor of decreased rehospitalization at 3 months (beta = -.58). Family ratings of conflict did not predict rehospitalization. A family emphasis on achievement predicted significantly fewer days of rehospitalization at 3 months (beta = -.20). Taken together with demographic and baseline measures of previous hospitalization, these family environment variables accounted for between 17% and 30% of the variance in rehospitalization at 3 months and 1 year. This study demonstrates positive aspects of family environment which predict lower rates of subsequent rehospitalization among psychiatric patients with thought, affective, and other major psychiatric disorders.

NR69 Wednesday, May 9, 10:45 A.M.

HARMFUL PSYCHOTHERAPY/CLINICAL STUDY OF 50 CASES

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Summary:

This paper will report the first extensive clinical interview study of patients who were harmed by psychotherapy. That psychoanalytic psychotherapy can have harmful effects is known to most clinicians, and is supported by a survey of psychotherapists conducted by Strupp, and by an analysis of the increased variance of measures of adjustment before and after treatment carried out by Bergin.

The sample comprises 48 mental health professionals who volunteered in response to an advertisement seeking subjects who had had a "harmful psychotherapy." The subjects described a total of 50 harmful therapies in one-and-one-half-hour interviews.

The harm to the patient was often long lasting, frequently years in duration, and led to increased anxiety, depression, impairment of functioning at work, loss of friends, alienation from family, and increased marital conflict. Most of the patients, however, remained protective of their therapists and felt loyal to him/her.

Analysis of data suggests that the cases were harmed in two main ways, either by therapies which were characterized as distant, cold, unengaged and lacking a "human quality" (18 cases), or by therapies in which the patient was involved in an intense emotional relationship (15 cases). These latter cases had three distinct different courses: 1) The patient was involved in a sexual relationship (4 cases), 2) A cult led by the therapist (4 cases), 3) They felt seduced by the therapist and then accused of having inappropriate feelings and left to manage their feelings on their own without psychotherapeutic investigation (7 cases). A residual group included five cases of poor match between patient and therapist, and 11 cases were less clearly classifiable.

The implications of the findings for research and clinical practice will be discussed.

NR70 Wednesday, May 9, 11:00 A.M.

COGNITIVE GROUP PSYCHOTHERAPY IN DEPRESSION

Lino Covi, M.D., Johns Hopkins Hospital, Meyer 2-181, 600 N. Wolfe Street, Baltimore, MD 21205; Ronald S. Lipman, Ph.D. (I), Philadelphia, PA; David Roth, Ph.D. (I), Joseph H. Pattison, M.D., James E. Smith, II, M.D., Baltimore, MD; Virginia K. Lasseter (I), Washington, DC

Summary:

Individual short term Cognitive-Behavioral Therapy (CBT), as developed by A.T. Beck, has been shown to be effective in depression. A group technique was developed augmenting the techniques of individual CBT with some group techniques. A pilot outcome trial compared CBT group alone, CBT group combined with open imipramine (IMI) administration and Traditional group alone. The therapists, two psychiatrists and a psychologist, were extensively trained, guided by written manuals and monitored by consultants. Two individual role induction visits were followed by 15 group sessions, a third individual visit was held after two group visits. Total treatment time was 14 weeks. An independent evaluator, blind to assignments, rated the subjects 3 times after the initial evaluation. Unimproved subjects who completed the 14 weeks of treatment were given four additional weeks of treatment and all improvers were followed up for 9 months.

Ninety-two Symptomatic Volunteers with Major Depression were randomized into treatment; 70 completed at least half the sessions, 53 completed the entire study. A full battery of self-rating and doctor-rated measures were employed. On most self-ratings and doctor's ratings CBT and CBT + IMI showed a significant advantage over Traditional; few differences were found between CBT and CBT + IMI. The difference continued over the 9 months of follow up. The rate of improvement obtained in this group CBT study compared favorably to that reported for individual CBT: 60% of the CBT-treated patients showed a complete remission of their depression. The finding of lack of improvement in traditional therapy confirmed that found in previous studies of open-ended traditional groups, but is limited to short term groups (14 weeks) homogeneous (for Major Depression) and without medication.

NR71 Wednesday, May 9, 11:15 A..M.

SYSTEM FOR RATING THERAPIES FOR DEPRESSION

Steven D. Hollon, Ph.D. (I), Department of Psychology, University of Minnesota, Minneapolis, MN 55455; Irene Elkin Waskow, Ph.D. (I), Rockville, MD; Mark D. Evans, B.A. (I), Minneapolis, MN; Alice Lowery, M.A. (I), Rockville, MD

Summary:

This presentation reports on the development of a therapy tape rating system to measure major dimensions of the treatment conditions in the NIMH Treatment of Depression Collaborative Research program (TDCRP). The TDCRP is a collaborative endeavor, in which three research sites are carrying out identical research protocols, studying the effects of two forms of brief psychotherapy (interpersonal psychotherapy and cognitive therapy) for outpatient, nonbipolar, nonpsychotic depression, and comparing these to pharmacotherapy reference and control conditions (imipramine plus clinical management and placebo plus clinical management).

There is a major emphasis in the TDCRP on the careful definition of treatment interventions, in order to allow for clear interpretation and replication of the findings. The effort to produce well defined treatments includes careful selection, training, and evaluation of therapists. In addition, it is necessary to assess the degree to which the therapists actually adhere to their respective treatment conditions and the degree to which the treatments can be differentiated from one another. The present scales, the Collaborative Study Psychotherapy Rating System (CSPRS), were developed for this purpose.

The system contains 88 items divided into three modality-specific domains, two nonspecific domains, facilitative conditions and directiveness, and two scales measuring approaches closely related to, but not components of, the two psychotherapies. Each of the three modality-specific scales is subdivided into content subscales tapping aspects of the respective therapies.

The instrument was developed in collaboration with the NIMH TDCRP coordinators, the expert trainers at the respective training centers, and the scale development team at the Universities of Minnesota and Pennsylvania. Initial item pools were developed and refined through a series of pilot studies, culminating in two successive generalizability studies involving tapes drawn from the training phase of the TDCRP and rated by naive raters blind to treatment modality.

Both generalizability studies indicated moderate-to-strong interrater reliabilities for the major scales, and adequate-to-strong reliabilities for the content subscales. Modality discrimination was consistently strong on the theoretically-specific scales, indicating that the three modalities could clearly be discriminated by independent raters. Classification based on discriminant function analyses indicated strong sensitivity and specificity for the instrument. Empirical factor analyses indicated that the original rational structure guiding scale construction was largely reflected in the empirical data.

Overall, the measurement system clearly differentiated and described the respective treatment modalities. Such a system can be used to assess adherence to treatment protocol and to describe the components of the respective treatment modalities in future research.

NR72 Wednesday, May 9, 11:30 A.M.

BRIEF DYNAMIC THERAPY OF BEREAVEMENT REACTIONS

Mardi Horowitz, M.D., University of California, Department of Psychiatry, Box 37B, 401 Parnassus Avenue, San Francisco, CA 94143, Charles R. Marmar, M.D., Daniel S. Weiss, Ph.D. (I), Kathryn N. DeWitt, Ph.D. (I), Robert Rosenbaum, Ph.D. (I), San Francisco, CA

Summary:

The relationship of dispositional and process variables with outcome was studied in a series of 52 bereaved patients treated with time-limited dynamic psychotherapy. Treatment outcomes were generally favorable, as reflected in two types of outcome: symptom relief and improvement in relationship and occupational functioning. Patients showed greater symptomatic improvement than change in social and work functioning. Pretreatment levels of impairment or distress were significantly related to outcome, but demographic and the majority of dispositional variables were not predictive of outcome. The process variables examined in relation to outcome were the therapeutic alliance and actions by the therapist. These process variables did not show statistically significant relationships with either type of outcome. When the same process variables were then considered in interaction with two dispositional variables, motivation for dynamic therapy and organizational level of the self-concept, statistically significant predictions of outcome were found. The major findings suggested that more exploratory actions were more suitable for highly motivated as well as better organized patients and less suitable for patients with lower levels of motivation or organization of the self-concept. Similarly, more supportive actions were more suitable for patients at lower dispositional levels and less therapeutic for patients at higher levels.

Poster Papers

NR73 Wednesday, May 9, 12 Noon-2:00 P.M.

PATHOLOGICAL GAMBLING AND MAJOR AFFECTIVE DISORDER

Robert D. Linden, M.D. (I), Harvard Medical School, Mailman Research Center, McLean Hospital, Belmont, MA 02178, Jeffrey M. Jonas, M.D., Harrison G. Pope, Jr., M.D. (I), Belmont, MA

Summary:

Pathological Gambling nas been variously viewed as an indication of personality disorder, related to substance abuse, or more recently as a variant of affective disorder. Winokur and colleagues noted an apparently high prevalence of pathological gambling in the families of bipolar probands. To further investigate this possible relationship, we performed a pilot study of the phenomenology and family history of 15 pathological gamblers.

Fifteen subjects were recruited from Gamblers Anonymous; all met DSM-III criteria for pathological gambling; no further inclusion or exclusion criteria were applied. After giving informed consent, the subjects received three separate interviews. One interviewer (RDL) administered the Structured Clinical Interview for DSM-III (SCID) by R. Spitzer and J. Williams, The second interviewer (JMJ) assessed the presesnce of six DSM-III axis II disorders, using a format similar to SCID. The third interviewer (HGP) assessed family history of psychiatric illness. Each interviewer was blind to the findings of the others.

Thirteen of the 15 subjects experienced an episode of major depression around the time that they first stopped gambling. Eight subjects experienced additional affective episodes; four of these subjects met criteria for bipolar disorder, and four for recurrent major depression. Five of these eight subjects also displayed panic disorder and/or obsessive compulsive disorder. Four subjects met DSM-III criteria for antisocial personality disorder. Family history results were inconclusive.

NR74 Wednesday, May 9, 12 Noon-2:00 P.M.

CLONIDINE BENEFITS CHILDREN WITH ATTENTION DEFICIT DISORDER AND HYPERACTIVITY: REPORT OF A DOUBLE-BLIND PLACEBO-CROSSOVER THERAPEUTIC TRIAL

Robert D. Hunt, M.D., Yale Child Study Center, 333 Cedar Street, New Haven, CT 06510, Rudi Minderra, M.D., Donald J. Cohen, M.D., New Haven, CT

Summary:

PURPOSE: Attention deficit disorder with hyperactivity (ADDH) is a frequent, serious disorder of childhood which does not universally respond to treatment with stimulant medications. Stimulants also have significant side effects including possible growth retardation, induction of tics, perservation, social withdrawal and diminished spontaneity. This double-blind placebo-crossover study explored the possible therapeutic utility of clonidine in children with ADDH.

METHOD: Ten ADDH children, ages 11.6 ± 0.54 (mean, SE) participated in a double-blind placebo-controlled cross-over with randomized sequence of 8 weeks of clonidine and 4 weeks placebo. The diagnosis of attention deficit disorder with hyperactivity (ADDH) was established using DSM-III criteria by two child psychiatrists following a standardized clinical interview with the parents and children (Diagnostic Interview for Children and Adolescents) and by behavior ratings (° 1.5 s.d. above normal on the Hyperactivity Index of the Connors' Teachers Behavior Rating Scale). Pretreatment physical, neuromaturational and cognitive assessment was performed. During treatment, children's behavior was quantified weekly by parents and teachers using the Connors' 48-item and 28-item scales respectively. At monthly intervals, children and parents returned to the clinic for follow-up assessment. Both child psychiatrists interviewed the parents and children on video tape and rated the child's behavior for DSM-III symptoms of attention deficit disorder. Children completed a self-report form. Neuromaturational and cognitive tests were also repeated.

RESULTS: Parent's ratings and narrative reports showed that 8 of the 10 children clearly benefited from clonidine. The mean behavior ratings for the group diminished from pretreatment levels of 65.00 ± 5.65 (mean, SE) to 43.00 ± 6.29 the end of active clonidine treatment ($p = 0.002$). Parents rated the greatest improvement in factors comprising the Hyperactivity Index, Conduct Problems, and Psychosomatic Problems. Teachers' rating showed that 9 of the 10 children improved with clonidine. Before clonidine treatment, teachers' sum scores were 45.75 ± 5.14 and decreased to 25.79 ± 1.31 by the last two weeks of active treatment ($p = 0.01$). The ratings on the "Hyperactivity Index" decreased even more significantly (1.85 ± 0.17 to 1.12 ± 0.06) by the end of active clonidine treatment ($p = 0.005$). Clinician ratings also supported the findings of clinical improvement. Performance on Coding and Digit Symbol tasks improved significantly. The major side effect was sleepiness which diminished in all but one child by the third week of treatment. Seven of the 10 children elected to remain on clonidine after completion of the study.

DISCUSSION: Clonidine appears to be a safe, effective medication for a subgroup of children with symptoms of ADDH. Studies are now in progress to systematically compare its effectiveness and clinical profile to methylphenidate. We will discuss the implications of a therapeutic response to clonidine for understanding noradrenergic mediation of the cognitive and behavioral symptoms of ADDH.

NR75 Wednesday, May 9, 12 Noon-2:00 P.M.

AGGRESSION IN CHILDREN OF HOLOCAUST SURVIVORS

John Sigal, Ph.D. (1), Department of Psychiatry, Jewish General Hospital, Montreal, Que., Canada H3T 1E2, Morton Weinfeld, Ph.D. (1), Montreal, Que., Canada

Summary:

Clinical studies suggest that children of survivors of the Nazi persecution exercise either too much or too little control over the expression of their aggression. The relevance of this finding to non-clinic populations was examined by comparing randomly selected samples of Jewish children of survivors (N = 242), children of other immigrant Jews (N = 76), and children of native born Jews (N = 200), all aged 19-36, on selected scales from the Psychiatric Epidemiology Research Instrument, and other variables related to the turning of aggression against the self or against others. No significant differences were found on the following variables: Active Expression of Hostility; Anti-Social History; Passive-Aggressive Behaviour; Rigidity; Guilt; Sadness; Self-Esteem; 8 out of 9 psychosomatic complaints; and Langner's 22-item scale scores. There was a non-significant trend for more death by suicide, homicide or accident to occur among children of survivors. Exposure to prolonged, severe victimization for ethnic reasons, or to other possible causes of Post-traumatic stress disorders, does not necessarily result in negative effects on the second generation in the area of the control of aggression, despite its long-term effects on the victims.

NR76 Wednesday, May 9, 12 Noon-2:00 P.M.

PERSONALITY VARIABLES AND EATING ATTITUDES

Andres J. Pumariega, M.D., Texas Children's Hospital, Post Office Box 20269, Houston, TX 77225; Joseph D. LaBarbera, Ph.D. (I), Nashville, TN

Summary:

There has been an increase in recent years in the number of studies that have attempted to assess the personality variables associated with anorexia nervosa. A serious problem with the vast majority of the reports involves the inferring of premorbid functioning based on evaluation of personality after the onset of the illness. It seems important that the existing studies of clinical subjects be augmented by research on subclinical and nonclinical individuals.

The present study examined the relation of certain personality variables to eating attitudes in a nonclinical group of 119 females age 16 - 18 years who were recruited from two large urban high schools. The personality variables included Perfectionism, Obsessionality, Achievement orientation, Separation difficulties, Body image, and Seuxal discomfort. Items for Obsessionality and Achievement were taken directly from the California Personality Inventory; those for the other scales were clinically derived. Final forms of the scales were determined by item analyses. Attitudes toward eating were measured by The Eating Attitudes Test, a 40-item rating scale that has been previously utilized in studies of eating disorders. In addition to overall scores on this instrument, factor analyses yielded six clusters of items for which each subject received a score: Weight anxiety, Eating anxiety, Dieting, Social pressure to eat, Dislike of food, and Somatic symptoms.

An interesting and coherent pattern of results emerged when correlational analyses were performed on the personality scales and the EAT clusters. For instance, Perfectionism was significantly associated with Weight anxiety, and Obsessionality was significantly correlated with Eating anxiety. The findings are discussed with reference to confusion in the eating disorders literature on the distinction between perfectionism and obsessive-compulsive traits. They are relevant also to the prevailing view of anorexia nervosa as a perfectionistic pursuit of thinness. Our results suggest that conflict about the eating function may also be operative - a finding that is reminiscent of the position of early psychoanalytic writers.

NR77 Wednesday, May 9, 12 Noon-2:00 P.M.

GASTRIC INHIBITORY PEPTIDE IN ANOREXIA NERVOSA

Katharine N. Dixon, M.D., Ohio State University, 473 W. 12th Avenue, Columbus, OH 43210, William Ziph, M.D. (1), T.M. O'Dorisio, M.D. (1), Samuel Cataland, M.D. (1), Columbus, OH

Summary:

Gastric inhibitory peptide (GIP), a gastrointestinal polypeptide, has an insulinotropic effect following ingestion of oral glucose or a meal. In addition, GIP has an inhibitory effect on gastric motility and acid secretion. Abnormalities in GIP response have been identified in diabetes mellitus, chronic pancreatitis, obesity, duodenal ulcer diease, and prolonged fasting or calorie-deficient states in healthy males. Subjective complaints of early satiety and post-prandial fullness in patients with anorexia nervosa (AN), validated in studies showing delayed gastric emptying and reduced acid secretion, interfere with nutritional rehabilitation in the AN patient. We studied simultaneous GIP, insulin and glucose responses to meal stimulation in 5 AN patients, 8 bulimics with a past history of AN (B/AN), and 22 normal controls. Serum concentrations of glucose, insulin, and GIP were measured at 0 time and between 5 and 180 minutes following a standard 250 calorie liquid meal since gastric emptying for liquids is reported to be normal in AN. Although basal levels of GIP (pg/ml) were similar, AN patients had an early and significantly higher ($p<0.05$) mean peak GIP response (2285±SE 152) than controls (1284±103) or bulimics with past AN (1303±150). Mean peak insulin (μU/ml) levels in AN patients (32±4) did not differ significantly from those of controls (37±5) or B/AN patients (26±3), although AN patients had a non-significantly prolonged elevation of serum insulin. Glucose responses were not significantly different among the various groups.

In conclusion, the exaggerated GIP response to meal stimulation with no significant difference in insulin levels suggests that the usual association between insulin and GIP is altered in AN. This is apparently a state-dependent abnormality since GIP responses in B/AN patients do not differ from normal controls. Altered GIP responses may contribute to the gastric motility and acid secretion changes previously reported in low-weight AN patients.

NR78 Wednesday, May 9, 12 Noon-2:00 P.M.

A CONTROLLED TRIAL USING DESIPRAMINE FOR BULIMIA

Patrick L. Hughes, M.D., Mayo Clinic, 200 S.W. First Street, Rochester, MN 55905, L.A. Wells, M.D., Carol J. Cunningham, M.S. (1), Rochester, MN

Summary:

Twenty-two patients completed a double-blind, placebo-controlled, trial using desipramine to treat bulimia. All patients fulfilled DSM-III criteria for bulimia, and did not suffer either major depression with melancholia or current anorexia nervosa. Duration of illness, symptom severity and degree of social dysfunction was quite heterogeneous.

Desipramine demonstrated a strikingly significant reduction in frequency and severity of bulimic symptoms, while placebo produced no change. Fifteen of 22 patients (68%) achieved total symptom remission. However, therapeutic benefit was generally attained within several days of reaching the initial standard dose of 200 mg. qhs. Individual dosages were adjusted to achieve therapeutic blood levels as needed, following the completion of six weeks of the double-blinded trial. No significant difference in therapeutic response was found between patient groups separated for statistical purposes on the basis of absence or presence of prior anorexia nervosa. Results of pre- and post-treatment DST's are reviewed.

This study strongly supports the recently advanced position of Pope, Walsh and others that antidepressants are highly effective in the treatment of bulimia. Secondly, the gratifying treatment response and the DST results lend further credence to the theory that bulimia is a discrete variant of affective disorder. Based on the striking similarity in our treatment response time to that achieved with imipramine in anxiety disorder with panic attacks, we proposed that bulimia and anxiety disorder with panic attacks may be closely related.

NR79 Wednesday, May 9, 12 Noon-2:00 P.M.

EATING DISORDERS IN AN ADOLESCENT POPULATION

David Greenfeld, M.D., Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510, Donald M. Quinlan, Ph.D. (I), Pamela Harding, M.A. (I), Elaine Glass, M.S.W. (I), Ann Bliss, M.S.W. (I), New Haven, CT

Summary:

The study explored the frequency of anorectic and bulimic behaviors in an adolescent school population, replicating and expanding an earlier study of college student. (Halmi, Falk, and Schwartz, Psychological Medicine, 1981, 11, 697-706). 424 males and 337 females ranging from 13 to 19 years of age and representing 83.5% of the total available population of a private New England preparatory school completed a questionnaire on eating disorders and related activities. Results: 28.1% of women and 10.0% of men reported they were concerned they might have an eating disorder. 81.4% of women and 26.2% of men reported that they often "feel fat". 45.9% of women and 17.1% of men describe themselves as overweight, although 6.9% of women and 17.3% of men are actually overweight by standard height-weight measures. 43.6% of women and 5.4% of men employ "crash diets" for weight reduction; 39.7% of women and 12.5% of men fast completely for more than a full day at a time in order to lose weight. 40.4% of women and 26.4% of men lost 10 or more lbs. during the previous year. 13.6% of women reported amenorrhea associated with weight loss. 64.5% of women and 24.9% of men acknowledge some symptoms of bulimia. Of the subjects who report binge eating, 29.4% of women and 19.5% of men do so while alone. 11.6% of women and 1.2% of men make themselves vomit after eating too much. 4.3% of women reported inducing vomiting once per week or more. 7.2% of the total subjects (14.1% of women and 1.7% of men) reported a range of bulimic behaviors which suggested they met DSM III criteria for bulimia. Factor analysis replicates to a large extent the findings of Halmi, et al of separate factors for bulimic and anorectic behavior. The incidence of these behaviors suggests a significant clinical problem in an adolescent school population. In this group of adolescent women in particular problems involving eating and morbid preoccupation with weight and body image appear to be widespread.

NR80 Wednesday, May 9, 12 Noon-2:00 P.M.

MISSED PHYSICAL DISEASE IN A MENTAL HEALTH SYSTEM

Lorrin M. Koran, M.D., Stanford University Medical Center, Department of Psychiatry, Room TD-114, Stanford, CA 94305, Harold C. Sox, Jr., M.D. (I), Keith I. Marton, M.D. (I), Stanford, CA

Summary:

We are investigating the prevalence of undetected physical disease in clients of California's public mental health system. The 500+ study subjects will be a random sample of patients treated in a state hospital; local inpatient units; outpatient clinics; day care programs; crisis intervention programs; psychiatric health facilities; skilled nursing facilities; and, community programs (e.g., board and care homes) in four counties. After receiving the mental health program's routine medical evaluation, each study patient is examined by a physician assistant (PA). The PA obtains a structured medical history, a complete physical examination, and blood for laboratory tests. These data are reviewed by an internist who decides whether to refer the patient for definitive diagnostic evaluation.

Of the first 300 study subjects, 143 (48%) were referred for definitive diagnostic evaluation. Of these 143, preliminary results indicate that 51 (35%) had previously undetected physical diseases that require treatment or continued medical surveillance and that were unknown to the mental health system. The 51 patients are 17% of the first 300 patients screened. The prevalence of previously undetected disease varies by program type: day treatment (12%); outpatient (17%); county acute inpatient (23%); community residential (33%); and, all others, excluding the state hospital, (10%).

In addition to physical diseases newly discovered by the Study, more than half (53%) of the 300 study subjects were found to have an active or possibly active physical disease that was being treated or probably required treatment. Of 43 chronic physical diseases being appropriately treated, only 24 (56%) were recorded in the client's mental health record.

Results for the first 400 patients will be presented with a breakdown of newly detected physical diseases into those causing, exacerbating or merely accompanying patients' mental disorders. The relative efficiency of each part of the screening evaluation (history, physical, lab) will be discussed.

NR81 Wednesday, May 9, 12 Noon-2:00 P.M.

ALIENATION AND DISABILITY AMONG INJURED POLICE

Alfred M. Bloch, M.D., 1830 West Olympic Boulevard, Los Angeles, CA 90006

Summary:

The author studied 177 law enforcement officers from 16 municipalities, referred for psychiatric evaluation and treatment for varying degrees of psychiatric dysfunction. All had previously sustained on-duty, partially disabling physical injuries and/or psychiatric disorders. Psychiatric evaluation, psychologic testing with treatment of 38, and follow up between 1978-1983, revealed that while 39 (22%) were able to return to police work, 138 (78%) were not, and sought disability retirement or different careers. Investigation of this phenomenon revealed psychodynamics which should provide insight into psychiatric sequelae of physical injury in this population.

Psychiatric evaluation revealed the officers' perception of the quasi-military organization as authoritarian and protective. They formed bonding relationships within this structure to insulate and defend against a hostile "outside" world. Unconscious needs for approval and assimilation required surrender of autonomy in favor of group identity. A high degree of cathexis was generally adaptive. Repression and denial were primary defense mechanisms.

All officers in this population had similar pre-morbid defense structures. Once injured, however, their defense mechanisms, already burdened with confrontation of physical injury, proved inadequate to deal with real or perceived rejection. The 138 officers who were not able to return to police work, experienced perceived loss of peer and administrative support. Access to continued medical treatment became difficult. Many were subjected to disciplinary actions, demotions and indictments of cowardice or malingering. Cathexis became maladaptive. They experienced feelings of existential isolation, betrayal and alienation. Resulting identity crisis required major psychic readjustment. Reactive depression developed with symptoms of mental impairment.

The 39 officers who returned successfully had similar pre-morbid defense structures, but described supportive environments. Results and focus of psychotherapy for this population are discussed, with specific recommendations for the treating or community psychiatrists. Suggestions to prevent or diminish this prenomenon are delineated.

NR82 Wednesday, May 9, 12 Noon-2:00 P.M.

PSYCHOSOCIAL ADJUSTMENT AFTER RENAL RETRANSPLANTS

Charlotte Nadel, M.D., SUNY-Downstate Medical Center, 450 Clarkson Avenue, Box #127, Brooklyn, NY 11203, Julian J. Clark, M.D., Brooklyn, NY

Summary:

This study was undertaken to see how the experience of a prior renal rejection affects patients' (pts.) psychologic adjustment to subsequent re-transplantation.

Pts. between ages 18-60 with non-diabetic renal failure, who had a second (or third) transplant at DMC more than one year prior were contacted, and 24 of 28 agreed to be interviewed. There were 15 pts. with a functioning kidney (F.K.) and 9 pts. back on dialysis (D.P.). Results showed that more F.K. were working (7 out of 15) than D.P. (2 out of 9). Sexual function decreased in 9 out of 15 F.K. and in 8 out of 9 D.P. Life satisfaction (L.S.), a global rating based on gratifications obtained from interpersonal relations, work and leisure activities, was good and very good in 7 out of 15 F.K. and 5 out of 9 D.P. pts.

Coping behaviors included denial, suppression, projection, internal control (control of physical discomfort via one's thoughts), activity (physical activity to divert dysphoric affects), feeling chosen (belief in being unique or specially selected to survive), and altruism. Pts. scoring low on L.S. ratings (12 pts.) tended to use denial (8 out of 12) and suppression (7) and projection (1) but made sparse use of other mechanisms. High L.S. pts. (12) used denial (8 out of 12) but also utilized many more of the other mechanisms. Three used altruism, 4 internal control, 8 felt chosen and 9 used activity. Good L.S. was present despite unemployment (5 out of 12), worsened financial state (8 out of 12) and decreased sexual functioning (4 out of 12). Half of the good L.S. pts. had decreases in 2 of these 3 categories. Unemployed men with high L.S. (4) took pleasure in "role reversal" activities such as cooking. Regardless of L.S. 6 out of 9 wanted another renal transplant.

In conclusion, half of both D.P. and F.K. pts. had good L.S. Denial was widely used but those who were better adjusted also utilized many other coping mechanisms. The rejection experience does not discourage most pts. from wanting another transplant.

NR83 Wednesday, May 9, 12 Noon-2:00 P.M.

PREDICTORS OF SMOKING CESSATION AFTER HEART ATTACK

Walter F. Baile, Jr., M.D. University of Maryland School of Medicine, Department of Psychiatry, 645 W. Redwood Street, Baltimore, MD 21201, George Bigelow, Ph.D. (1), Thomas Burling, Ph.D. (1), Cynthia Rand, Ph.D. (1), Sheldon Gottlieb, M.D. (1), Albert Jerome, M.A. (1), Kenneth Kolodner, M.A. (1), Baltimore, MD

Summary:

Continued cigarette smoking after myocardial infarction doubles the risk for subsequent cardiac morbidity and mortality. In order to study the extent to which heart attack patients quit smoking and factors associated with successful cessation we conducted two prospective studies.

In the first we followed 107 hospitalized survivors of acute myocardial infarction. All were chronic cigarette smokers none of whom smoked during the first several days of treatment. They were seen daily throughout their hospitalization and followed up for 1-2 years after hospital discharge. Smoking status was assessed at each contact by self-report and by breath carbon monoxide, an objective measure of smoking. In 68 patients left ventricular ejection fraction (LVEF), a measure of cardiac pump performance, was determined using a nuclear medicine procedure.

Results showed that over a 1-2 year follow-up only 22.4% attained long term smoking abstinence. This was more likely among white males experiencing their first heart attack (15/42, 35.7%) than among all other patients (9/65, 13.5%) a difference significant at p. 01. Relapse was also less likely in those with more impaired cardiac pump function as measured by mean LVEF (0.48 vs. 0.36, $p<.004$).

A second study of 71 patients using a similar prospective design included measurements of attitude and personality prior to relapse and determined their predictive value. Early (in-hospital) smoking resumption occurred in 16% of patients and was associated with high premorbid level of alcohol use ($p<.001$), negative attitudes towards quitting ($p<.001$) and depressed affect ($p<.05$). Successful in-hospital abstainers were more likely to be influenced in quitting by spouses and friends ($p<.005$) and to have an external Health Locus of Control (HLC) ($p<.03$). As follow up continued factors relating to prior smoking habits and impulsive personality traits became significant predictors of relapse while family influence and HLC remained significantly associated with abstinence.

These studies define important correlates and predictors of continued tobacco dependence in a high risk population. They confirm our previous work (Addictive Behaviors, 1983) suggesting that smoking cessation may be highest in those most likely to benefit and that the benefits of cessation might be underestimated since patients with the worst cardiac performance had the highest quit rate.They indicate that a strong relationship exists between relapse, abstinence and several psychosocial factors, especially alcohol abuse and social relationships. Moreover, at different points in time of relapse different predictive variables are important. We hope that these findings will allow the design of intervention studies.

NR84 Wednesday, May 9, 12 Noon-2:00 P.M.

THE LANGUAGE OF SOMATIZATION

Thomas E. Oxman, M.D., Dartmouth Medical School, Department of Psychiatry, Hanover, NH 03756, Stanley D. Rosenberg, Ph.D. (I), Gary J. Tucker, M.D., Hanover, NH

Summary:

Somatic complaints and depressed mood are ubiquitous symptoms that often occur together. In their extreme forms, Somatization Disorder (SD) and Major Depressive Disorder (MDD), clinical discrimination is difficult. With the advent of computerized content analysis, we have shown that differentiation of clinical disorders by their verbal presentation is now explicitly possible. In this study computerized content analysis was used to answer two questions: 1) Do the verbal themes of patients with SD distinguish them from patients with MDD? 2) What do the verbal patterns of SD and MDD lend to the theory and understanding of these disorders?

METHOD: Computerized content analysis was applied to free speech samples of 62 patients in four diagnostic groups: SD (n=11, depressed mood in 9); MDD (n=11); Cancer or Myocardial Infarction (n=16); or Psychotic Disorders (n=24). The first 600 words of each patient were grouped by computer into frequency of the 83 categories of the Harvard III Psychosocial Dictionary.

RESULTS: Twenty-one categories demonstrated group differences ($p < .05$) in word frequency. Among these the "negative" ($F=43.3$, $p < .00001$) and the "identity" ($F=19.8$, $p < .00001$) categories most highly distinguished SD from all other groups while the "lower status" ($F=7.66$, $p=.0002$) and the "neutral role" ($F=5.1$, $p=.0035$) categories separated MDD from the other groups. The "small group" ($F=4.1$, $p=.01$), "community" ($F=5.9$, $p=.001$), and "family" ($F=4.9$, $p=.004$) categories differentiated MDD from SD.

SIGNIFICANCE: The language used by the SD's strikingly separates them from MDD's and, moreover, conveys an overwhelming negativism and uncertain self-identity, e.g. "I am NOT able, NOT have friends, I do NOT know," and, "I AM going off deep, AM scared, AM going to fall, AM afraid, AM confused, AM tense." In MDD the identity category is more positive and certain, e.g. "accept who I AM, that's who I AM." Also, the language patterns distinguishing MDD deal with their relations with others, e.g. "friend, people, visit, sons," a connectedness lacking in SD patients. The language of Somatization Disorder reflects thought processes influenced far more by factors other than simply bodily preoccupation or depression. This technique shows how word frequency has meaning and the impact this has on the clinician. Contrary to alexithymia, SD speech shows not suppression of emotions, but expression of a confused emotional deluge.

NR85 Wednesday, May 9, 12 Noon-2:00 P.M.

PSYCHIATRIC CORRELATES OF ASBESTOS EXPOSURE

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Summary:

Increasingly frequent environmental exposures to hazardous substances present mental health professionals with individuals at increased medical risk and many who are already physically ill as a result of such an exposure. A study has been undertaken to evaluate the psychiatric correlates of chronic occupational exposure to asbestos, one of the most pervasive carcinogens in our environment, by administering standardized and specially-devised assessment measures to: 1 - 111 pipecoverers, who having worked occupationally with asbestos for the past 20 years, are now at increased medical risk; 2 - 36 patients with a diagnosis of diffuse malignant mesothelioma, a cancer singularly related to asbestos exposure; and, 3 - 48 postal workers, who represent a blue collar comparison group, without known occupational hazardous exposure. In comparison to the postal workers, pipecoverers did not exhibit elevated levels of psychopathology on the current section of the Current and Past Psychopathology Scales (CAPPS). In comparison with these two groups, mesothelioma patients had significantly more depressed and anxious mood states ($F=11.88$, $p<.0001$), more concern about their health ($F=11.07$, $p<.0001$), and higher levels of guilt ($F=3.05$, $p<.05$). Forty-five percent of mesothelioma patients received a computer-derived diagnosis (based on DSM II) of a depressive disorder compared to only 14% of the asbestos workers, and 6% of the comparison group. Psychiatric evaluation of the past, did not reveal differences between the three groups on such factors as prior utilization of mental health services, use of tranquilizers, incidence of alcoholism, and divorce rate. There was a singular lack of adaptive health promotive behaviors on the part of the increased risk group such as smoking cessation (32% of the asbestos workers continued to smoke despite the strong synergistic effect between smoking and asbestos), usage of masks (worn only 9% of the time), and regular physical exams (43% never went). The low incidence of present and past psychiatric morbidity in the medical risk group along with the nonadaptive health behaviors may indicate that denial of risk is a predominant coping mechanism for individuals at chronic increased cancer risk. Asbestos-exposed individuals therefore may have a strong need for psychiatric intervention in the at risk phase to diminish the denial and increase health promotive behaviors and to cope with the frequently encountered depressive disorders in the illness phase[1]

NR86 Wednesday, May 9, 12 Noon-2:00 P.M.

QUALITY OF LIFE SIX MONTHS AFTER CORONARY BYPASS

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Summary:

We report on quality of life six months postoperatively in 96 patients who underwent coronary artery bypass grafting (CABG). This ongoing study of outcome from CABG surgery utilizes the Psychosocial Adjustment to Illness Scale (PAIS), a brief but comprehensive measure of quality of life. Patients who were administered the PAIS 2 days preoperatively and 6 months postoperatively showed significant improvement in overall quality of life at follow-up ($p < .0006$). Of interest, we found significant improvement in both sexual function and vocational status. Unexpectedly, elderly CABG patients showed less psychological distress than younger patients.

The seven subscales of the PAIS reflect adjustment to illness in several quality of life domains: sexual function, vocational status, domestic environment, extended family relationships, social activities, psychological distress, and health concerns. Our patients showed an improvement in four areas, no change in two areas, and a decline in one area. The significant improvement at 6 months postoperatively shown in sexual function ($p < .02$) and vocational status ($p = 0.0001$) is at variance with previous outcome studies. We also noted that CABG surgery was followed by significant strengthening of relationships within the nuclear family and in social activities ($p = .0001$). No change, however, was found in overall relationships with the extended family ($p= .60$) or in psychological distress for the group as a whole ($p = .20$). The only significant decline was in health concerns shown by our finding that CABG patients are less satisfied with health status six months postoperatively ($p = .0001$).

Surprisingly, increased age was associated with decreased psychological distress at six months ($p < .02$). In addition, age was not associated with worsened outcome on any of the other six subscales. This finding is contrary to those studies which suggest that increasing age confers greater risk of poor adaptation to the surgery.

In general, our patients improved in psychosocial function in a manner consistent with the recent studies of outcome from CABG surgery. In contrast with other studies, however, our patients showed improved adjustment in sexual function and in vocational status.

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CHRONIC PAIN, DEPRESSION AND ALCOHOLISM

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Summary:

Our previous studies of patients with chronic pain in the absence of a somatic cause had led to the identification of a well-defined psychobiological disorder termed the Pain-Prone Disorder. This syndrome is viewed as a variant of depressive disease. The psychological and biological characteristics of the Pain-Prone Disorder were examined by comparing 66 pain-prone patients to a first control group of 55 hospitalized patients with primary depressive disease and to a second control group of 55 alcoholics in their fourth week of hospitalization, i.e., two well established affective disorders.

Data were collected from the three groups of patients across four classes of variables: (1) clinical - Hamilton Psychiatric Rating Scale for Depression (HPRSD), Questionnaire for Pain Syndromes; (2) genetic - Family History/Research Diagnostic Criteria; (3) other biological - dexamethasone suppression test, urinary MHPG, urinary cortisol, polysomnogram; and (4) psychodynamic - SEDD.

Although 58% of the depressed patients and 38% of the alcoholics complained of chronic pain, their pain was neither continuous nor disabling. The pain-prone patients differed significantly from both other groups by anergia and anhedonia. Marked denial of emotional and interpersonal conflicts was manifested to a significant degree by both pain-prone patients and alcoholics. On the HPRSD pain-prone patients scored abnormally high ($\bar{x}$ = 25.36), similar to the depressed patients ($\bar{x}$ = 26.56) and significantly higher than the alcoholics ($\bar{x}$ = 7.73). Family histories revealed significant numbers of 1^{o} relatives with chronic pain and unspecified psychiatric disorders among the pain-prone patients; significant numbers of 1^{o} relatives with depressive disorders among the depressive control group; and significant numbers of 1^{o} alcoholic relatives among the alcoholic control group. Only the depressed patients showed abnormal values on each of the biological markers; the alcoholics' values were all normal; and the pain-prone patients had borderline shortened REM latency and lowered MHPG values. Psychodynamically, the pain-prone patients manifested significant trends of masochism, neurotic ego patterns and infantile dependency needs.

The findings indicate a close kinship of the pain-prone and depressed patients, while alcoholics in the recovery phase were free from the measured signs of depressive disease.

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PSYCHIATRIC INTERVENTION IN SOMATIZATION DISORDER

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Summary:

Patients with somatization disorder have been observed clinically to utilize an excessive amount of health care resources. This study documents the amount of care consumed by patients with this disorder and reports a cost effective consultation/liaison intervention resulting in a dramatic reduction in health care utilization. Patients who met the essential features of somatization disorder and who were cared for by primary care physicians were referred for study. After thorough evaluation, 38 were entered into the study and randomized to treatment and control groups according to primary physician. The groups were not significantly different on most parameters. Health care utilization was meticuously analyzed for two and one-half years prior to entry as a baseline. The physicians of the treatment group received detailed consultation letters from the consulting psychiatrist outlining recommendations for management and describing the disorder. The control physicians received letters thanking them for allowing the patient to be seen.

During the 9 month study period the mean total health care charges were $1,319 for the treatment group compared to $4,972 for the control group ($p = .05$). The treatment group's mean total health care charge was reduced from $2,307 for the preceding three 9-month periods to $1,319 ($p < .05$), while the control group's charge rose from $2,747 to $4,972.

These savings were accomplished without significant changes in any of seven mental health measures employed, including anxiety and depression, changes in measures of physical health, social health, or the patients' perception of their health. Further, the interventions were accomplished by standard C/L recommendations, thereby providing evidence for the cost effectiveness of psychiatric intervention in patients with somatization disorder.

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SOCIAL DYSFUNCTION IN SOMATIZATION DISORDER

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Summary:

Fifty female patients with somatization disorder by DSM-III criteria (and Briquet's syndrome by Feighner criteria)and 25 age and race matched female patients with primary unipolar major depression were compared for variables related to diagnosis, social dysfunction, psychiatric symptoms, and medical problems. An objective measure of social dysfunction using disability payments, the loss of custody of a child, loss of a job due to medical or psychiatric symptoms, and being unable to care for the home showed 66% of the somatizers with at least one of the above compared to 40% of the women with major depression; 30% of the somatizers had two or more of the above compared to 12% of the women with major depression. 52% of the somatizers met criteria for major depressive disorder; the presence of major depression did not affect the degree of social dysfunction or the severity of medical problems. The somatizers had three times the number of operations and hospitalizations as the women with major depression. Only sixteen somatizers were diagnosed on the first visit and in 21 women somatization disorder was not even suspected. It took six visits on average before the diagnosis of somatization disorder was made. The presence of major depression did not affect the difficulty of diagnosis but the presence of other psychiatric symptoms(e.g. antisocial, anorexic, bulimic, obsessive, panic) did. The presence of other psychiatric symptoms did not significantly correlate with social dysfunction or medical problems. Medical problems were only weakly correlated with social dysfunction. We concluded that (1) women with somatization disorder also have numerous psychiatric symptoms and meet criteria for other psychiatric diagnoses, including major depression, (2) these symptoms confound the diagnosis initially, (3) the presence of multiple somatic complaints and a complicated medical history are reliable diagnostic criteria. Somatizers have numerous social problems and are disabled in their roles as workers, mothers, and wives. This disability is only partially explained by their medical problems. The presence of major depression does not explain either social dysfunction or their somatic symptoms but is a frequent complication.

NR90 Wednesday, May 9, 12 Noon-2:00 P.M.

THE PSYCHOSOCIAL ASPECTS OF AIDS

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Summary:

We report psychosocial data on thirteen patients hospitalized with AIDS. Assessment included psychiatric interview and chart review, MMPI, Hamilton Rating Scale, Symptom Self-Rating Scale (SCL-90) and Karnofsky Scale of Physical Performance Status. Five patients had both Kaposi's sarcoma and Pneumocystis carinii pneumonia, seven had Pneumocystis alone and one had cryptococcal meningitis. All had a syndrome of malaise, lymphadenopathy, fever and weight loss. Nine had Karnofsky scores of sixty or less, reflecting marked physical disability. Ten males were active homosexuals with promiscuous sexual behavior; the other male was the heterosexual partner of an IV drug abuser. The two females had histories of IV drug abuse and prostitution. Social impairment was common: although twelve patients were employed prior to illness, all were currently unable to work. In addition, most reported a high degree of social isolation. Four patients had consulted a mental health professional regularly in the past, two for affective disorders and two for substance abuse. Nine (69%) had DSM III diagnoses of adjustment disorder with depressed anxious or mixed features; one also had an atypical organic brain syndrome. Six had histories of substance abuse. Three (23%) had Hamilton scores in the very depressed range (>25). Scores on the SCL-90 revealed a high degree of anxiety and subjective cognitive impairment. Elevation was found on MMPI sub-scales for depression (82%), masculinity-femininity (73%), hysteria (64%) and hypochondriasis (55%). Forty-five percent had elevations on the psychopathy, psychasthenia and schizophrenia sub-scales. Thus, our results demonstrate significant psychosocial morbidity in this group of AIDS patients. Although it is unclear to what degree morbidity antedates, or is a direct consequence of the illness, our findings emphasize the importance of further psychosocial assessment and appropriate intervention in these multiply handicapped patients.

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ATTITUDES OF DOCTORS AND NURSES TOWARD HOMOSEXUALS

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Summary:

In the setting of the AIDS epidemic, negative attitudes toward homosexuals have become more prominent in the general population. There have also been numerous anecdotal reports of prejudicial attitudes and behavior toward homosexual AIDS patients among health professionals. In some medical centers, AIDS has been called the gay plague, SQWID (sick queers with immune deficiencies) or WOG (wrath of God). Such anecdotes suggest the AIDS epidemic has activated underlying anxiety concerning homosexuality and not simply fear of contagion. The purpose of this preliminary study is to investigate and quantify for the first time the degree of homophobia among physicians and nurses working in a large, urban teaching hospital. For the purposes of this study, homophobia is defined as the constellation of affective responses including fear, disgust, anger, discomfort and aversion that individuals experience in contacts with homosexuals. Methodology: All house officers (n=91) and registered nurses (n=261) in the department of Medicine of the New York Hospital were given the Index of Homophobia scale. This is an anonymous, self-administered Likert-type instrument, the validity and reliability of which have been previously established. The scale is designed to provide a numerical measure of an individual's homophobia (range 0-100, with scores greater than 50 defined as homophobic); demographic data (sex, age, religion, etc.) were also obtained. Results: 41% of physicians and 35% of nurses returned questionnaires. The mean scores for both groups fell in the low-grade homophobic range (50-75) as defined by the study instrument. Although there was no significant difference in mean scores between doctors and nurses, female respondents were significantly more homophobic than males (56.09 vs. 49.76, $t=2.08$, $p<.05$). This is in contrast to many earlier studies demonstrating greater homophobia among males. Physicians who stated they have a close friend or relative who is homosexual had significantly lower mean scores than those who did not. There was no significant difference in measured homophobia between Catholics and Jews, or between respondents who practice their religion and those who do not. Prior studies have generally found Jews to be more permissive than other religious groups, and regular church attenders more likely to reject the legitimacy of homosexual relations. Additional data will be presented. The study demonstrates that levels of homophobia among health professionals can be quantitatively determined.

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COGNITIVE AND/OR PHARMACOTHERAPY: ONE YEAR LATER

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Summary:

Seventy patients who had completed a 12 week course of either cognitive therapy, pharmacotherapy, cognitive therapy plus active placebo, or cognitive therapy plus pharmacotherapy were followed at one month, six month and one year intervals after termination of active treatment. Of the 44 patients who had originally responded to treatment, 28 of them remained well during the one year followup period. Sixteen patients experienced a relapse or recurrence of depression as defined by reentry into treatment for depression of self-reported or interviewer-rated depression scores in the depressed range. Patients who had received cognitive therapy were significantly less likely to relapse than patients who had no exposure to cognitive therapy.

Vulnerability to relapse was examined by looking at characteristics of the depressive illness as well as status on psychosocial variables at the termination of treatment. There was no association between number of previous episodes or age and the subsequent reappearence of symptoms. Instead, in this sample, patients with good social adjustment and high self control skills at termination were significantly less likely to relapse. In contrast, high levels of dysfunctional attitudes significantly increased the probability of reappearence of depressive symptoms.

Patients who had initially not responded to treatment were also followed. A large proportion of this group (62%) of 26 patients sought further treatment. Another 23% still had BDI scores 16 at one month followup. By one year followup however, the mean BDI and HRSD scores for the nonresponder group fell within the nondepressed range.

Discussion of these results focuses on the possible mechanisms of the prophylactic effect of cognitive therapy and the need for a multivariate model of vulnerability to relapse. Finally, the significance of these followup data to the understanding of the natural course of depressive illness is presented.

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EXPRESSED EMOTION AND RECOVERY FROM DEPRESSION

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Summary:

This prospective study of the influence of social support upon the post-hospital course of depressed women included the Camberwell family interview and ratings of expressed emotion. The only reported study using this methodology with depressed rather than schizophrenic patients found that the number of critical comments made by the spouse was the best single predictor of symptomatic relapse (Vaughn and Leff, 1976).

A sample of 49 married women who met R.D.C. for Major Depressive Disorder was obtained from the inpatient units of several general hospitals. Several ratings of the marriage and a count of the number of critical comments about the partner were based upon separate, taped semistructured interviews with the patient and spouse at the time of admission. Six months later both partners were reinterviewed separately and symptom course was rated using the L.I.F.E. psychiatric status schedule.

Only 51% of the sample recovered from the depressive episode in the follow-up period. Although the ratings of the marriage based upon the woman's account did predict symptom course, for the most part those based upon the interview with the husband did not. In particular, the hypothesis that the level of expressed criticism by the spouses at the time of admission will predict post-hospital outcome was not supported.

The low rate of recovery is consistent with other studies of major depressive disorder which suggest that short-term prognosis may not be as positive as is commonly thought. Possible explanations of our failure to replicate the findings of the British study will be explored. Even though the specific hypothesis is not supported, the findings are generally consonant with the assumption that the quality of the marital relationship influences symptom course.

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PSYCHOSOCIAL STRESS PREDICTS TRICYCLIC ANTIDEPRESSANTS' RESPONSE

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Summary:

Objective: Current levels of psychosocial stress (DSM III-Axis IV) were compared between responders and nonresponders to tricyclic antidepressants in a sample of non-delusional, hospitalized depressed patients.

Methods: 86 depressed patients with DSM III-Major Depressive disorder were treated for 3-6 weeks with flexible dosages (150-300 mg range). Patients with delusions (N=20) or steady-state plasma drug concentration in the lowest quartile (N=21) were excluded from the analysis. Therefore, the current sample includes 45 patients treated with imipramine (N=15), amitriptyline (N=16) or desipramine (N=14). All patients were rated using the Hamilton Depression Scale and DSM III Axis IV. Plasma TCA concentrations were determined by a GC Method. Favorable response was defined as a final HAM-D $\leq$10 with at least a 50% reduction from baseline.

Results: 23 patients were classified as responders and 22 as nonresponders. Response rates did not differ significantly among the three drugs. Moderate to severe psychosocial stress (Axis IV rating IV-VI) was present in 5/23 responders and 16/22 nonresponders (x^2=10.6, $p < .01$). Major categories of psychosocial stress among nonresponders included: disruption of family or social network (N=7), death of close relative or spouse (N=6), vocational/financial problems (N=4) and Family illness (N=2).

Significance: Although a number of previous investigators have reported on life events which precipitate depression as factors in treatment outcome, surprisingly little work as examined current level of psychosocial stress as an outcome variable. One exception is the report of Akiskal (1), which found recent death and illness in relatives to be associated with chronicity of depression. Our results suggest that when delusions and inadequate plasma drug, levels are eliminated as confounding factors, DSM III-Axis IV strongly predicts response to TCA's in hospitalized Major Depressions.

If confirmed in other patient samples, this finding may have important therapeutic implications for differential treatment selection. Non-delusional patients with high current psychosocial stress may be a particular target group for combined chemotherapy and psychotherapy.

Akiskal, H.S.: J. Clinical Psychiatry, 43:266-271, 1982.

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MAJOR DEPRESSION AND FAMILY FUNCTIONING

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Summary:

There are very few studies that have assessed the functioning of families of patients with major depression. Existing studies have tended to assess single dimensions of family health or pathology and have used subscales of instruments designed for purposes other than to measure family functioning. The goal of the present study was to assess family functioning during an acute episode of major depression using a multidimensional family assessment instrument. Family functioning in 43 consecutive consenting families with one member meeting DSM-III criteria for major depression were compared to 29 families without any current or past history of psychiatric illness. The depressed patients were inpatients in a short-term psychiatric facility. At least two family members in each family completed the Family Assessment Device, a 60-item self-report questionnaire with seven scales assessing general family functioning and the six dimensions of the McMaster Model of Family Functioning (problem-solving, communication, roles, affective involvement, affective responsiveness, behavioral control). Demographic variables including age, socioeconomic status, income, religion, number and age of children, education, marital status, number of years married and role of the patient in the family were collected for all families. Analyses of variance compared the two groups on each of the scales of the FAD using mean family scores. All demographic variables which differed between groups were included as co-variants.

Comparison of FAD scores of depressed and control families indicated that the families in the depressed group reported significantly more disturbed functioning on two scales, problem-solving ($F=7.11$; df 1,66; $p<.01$) and communication ($F=9.29$; df 1,66; $p<.005$). Communication tended to be more impaired in those families where the mother was a patient. These results suggest that during an acute episode of major depression families perceive significant dysfunction in some aspects of their family life, communications and problem solving, but not in others, and that these differences can be measured selectively. It appears that the obtained differences are not due to a general response bias or dysfunction of depressed families, but rather represent specific areas of difficulty. These findings also have potential clinical significance in focusing therapeutic interventions on those areas of family functioning known to be creating the greatest difficulties for families with depressed members.

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DSM-III VERSUS PROBLEMS AS PREDICTORS OF TREATMENT

Richard Longabaugh, Ed.D. (1), Butler Hospital, 345 Blackstone Boulevard, Providence, RI 02906, Robert Stout, Ph.D. (1) George Kriebel, Jr., M.D., Leigh McCullough, Ph.D. (1), Duane Bishop, M.D., Providence, RI

Summary:

In a previous study we compared clinically identified problems with DSM-III diagnoses as predictors of treatment (Validation of a Problem-Focused Nomenclature, Archives of General Psychiatry , Vol 40, April 1983). We found that problems were better predictors of treatment and outcome than were DSM-II diagnoses. Since that study, DSM-III has replaced DSM-II. The present research compares clinically identified problems with DSM-III as predictors of treatment. The question we seek to answer is to what extent DSM-III diagnoses and problems, alone, and in combination are related to treatment interventions. To the extent that they are so related they give evidence of fulfilling one of the functions of a diagnostic nomenclature, helping clinicians to decide on appropriate treatment interventions.

Patient problems, treatments, and DSM-III Axis I and II diagnoses were coded from the problem oriented records of 652 patients randomly selected from admissions to an acute psychiatric hospital. ($\bar{x}$ LOS = 18 days). Problems and diagnoses were used separately to predict 24 treatment interventions, with stepwise multiple regression analyses. Problems and diagnoses found to be significant predictors of a treatment were then both entered into a single regression analysis. To test whether problems or diagnoses added significant predictability beyond diagnoses (problems) we partialled out the effects of each. Results indicated that DSM-III diagnoses and problems are robust and equally useful in accounting for medication treatments. (Explained variance ranged from 27 to 47%). Combined, they accounted for significantly more of the variance. In predicting psychosocial interventions, both problems and diagnoses are much less useful. Problems are ordinarily more useful than DSM-III diagnoses, however, the combination of problems and diagnoses were usually the best predictor set. In comparison with the earlier study, both problems and DSM-III predict more of the variance in medication treatments and less of the variance in psychosocial interventions than did problems and DSM-II diagnoses.

More detailed analyses of the ways in which problems enhance predictability beyond that afforded by diagnoses suggest that: (1) further refinement of diagnoses should increase their value in providing rationale for treatment, and (2) Axis IV of the DSM-III, psychosocial stressors, should be greatly elaborated to provide articulation comparable to that of DSM-III Axes I-III. These steps would enhance the value of the DSM-III for clinicians.

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EARLY THERAPY TERMINATION: PATIENTS' PERSPECTIVES

Karla Moras, M.A. (I), Connecticut Mental Health Center, 34 Park Street, New Haven, CT 06508, William H. Sledge, M.D., Dianna Hartley, Ph.D. (I), New Haven, CT

Summary:

Patient unilateral withdrawal ("dropout") was examined in 158 community clinic outpatients who had moderate to excellent potential to benefit from psychotherapy. Good therapy candidates were studied based on the rationale that clinically useful findings were most likely from patients judged able to benefit from psychotherapy, but who dropped out. The main hypothesis was that patient dropout in the initial phase of therapy ($\leq$six sessions) indicates treatment failure: i.e., the person feels therapy is ineffective or has a more negative reaction to it.

A retrospective follow-up design was used. The identified sample consisted of new clinic patients who were referred to individual therapy during a 1 1/2 year period, and who had been discharged since then. Criteria commonly used in clinic settings were applied to charts to screen out patients who were poor prognostic risks for individual psychotherapy (e.g., DSM-III, Axis I, Alcohol Abuse). The data consist of standard and original self-report questionnaires (e.g., Client Satisfaction Questionnaire), and semi-structured phenomenological interviews, audiorecorded with consent, in which respondents described their therapy experiences. The questionnaires include indices of outcome, satisfaction, personality, and reasons for dropout posited in the literature. Patient self-reported reasons for ending therapy were obtained in open-ended questions, and in the interview.

The respondent sample was 66 (respondent rate 41%). Analyses will be done to examine the extent to which nonrespondent and respondent dropouts might differ on the main variables such as outcome. Hypotheses will be tested by comparing the self-report indices of outcome, satisfaction, and reasons for leaving from several patient groups. The groups are defined both by phase and manner of termination, e.g., dropped out in initial phase of therapy, dropped out after initial phase, or remained to a preset termination date. A preliminary impression is that the main hypothesis was confirmed: Patients who dropped out of therapy in the initial phase primarily left due to dissatisfaction with the therapy/therapist. By contrast, it appears that patients who dropped out later, particularly near a preset termination date, left "first" as a way of mastering strong feelings of attachment toward the therapy/therapist. Hypotheses generated from the interviews on factors that contribute to patient dropout will be discussed in the paper. Prospective studies of hypotheses from the study are planned.

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AN EMPIRICAL STUDY OF DIAGNOSIS AND DEFENSE STYLE

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Summary:

The relationship between DSM-III Axis I, II and IV diagnoses and defense style was studied in a sample of 74 psychiatric patients. The subjects completed a self-administered questionnaire composed of 81 statements about behaviors, thoughts, and feelings. The statements were designed to reflect various unconscious defense mechanisms. The patients responded by rating on a nine point scale the degree to which each statement applied to them. Factor analysis of the responses revealed four defense styles ranging on a continuum from primitive to mature. Patients' defense styles were compared with their diagnoses on axes I, II and IV of DSM-III. No significant relationship was found between defense style and diagnosis, suggesting that diagnosis and defense style are two independent dimensions. Since DSM-III diagnosis does not predict defense style, a sixth axis reflecting psychodynamic formulation would provide additional information necessary for therapeutic planning.

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A NEW BEREAVEMENT SCALE

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Summary:

Major medical illnesses with elevated rates of mental disorders and mortality rates up to 4 times control rates have been reported following bereavement, but the lack of a simple scale to assess grief severity has limited the study of the pathogenic role of grief. Thus we constructed an 18 item self report scale to quantify two aspects of grief: emotional numbness (EN) and separation anxiety (SA) from a lost or ill family member. The 6 EN items included feeling numbness, disbelief, dread and loss of control (score range= 0-18) and were expected to be endorsed by B who manifested little response to the loss. The 12 SA items included yearning, sighing, crying and sensory illusions about the lost person (range= 0.36). Psychiatrists' ratings of pining (P) and emotional response (ER) to the loss in 40 spousally bereaved (B) older men and women were highly correlated with SA (r=0.71 for P, r=0.74 for ER). As expected, these overt manifestations of distress had no correlation with EN (r=0 for P, r=0.14 for ER). The scales also had excellent internal reliability and were able to discriminate B (n=66) from a highly stressed control group whose spouse was expected to die, but did not (n=32). As expected in the normal course of grief, EN decreased among the B from 6.2 at the time of the death to 1.0 at 6 months after the loss, but SA remained relatively unchanged throughout the 6 months going from 12 at 1 month to 9 at 6 months after the loss. Thus, our new grief scales could discriminate bereaved older people from other persons under stress, and they had high internal reliability and concurrent validity compared to psychiatrists' ratings. EN also had its expected response decrement over time, while SA remained prominent. We conclude that these scales can be used to now study the relationship of loss and grief to medical illness.

NR100 Wednesday, May 9, 12 Noon-2:00 P.M.

INTERMITTENT EXPLOSIVE DISORDER: A MYTH?

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Summary:

DSM-III criteria for the diagnosis of Intermittent Explosive disorder includes discreet loss of control of aggressive impulsives and the absence of more pervasive psychopathology such as generalized impulsivity or aggressiveness. The present study compares a group of patients diagnosed as Intermittent Explosive Disorder (IED) with a group of non-patients (NP) in order to validate the diagnostic criteria. There were 56 IED subjects, of which 50 were males. The NP group contained 122 controls of which 61 were males. Data analysis was carried out only on male subjects and controls. In addition, EEG data from the IED group was compared with similar data obtained from 45 normal controls. Two instruments were used: 1) Neuropsychiatric inventory, a questionnaire developed by Dr. Balis, which collects self-reported clinical information in areas such as paroxysmal and non-paroxysmal symptoms, history of brain injury, history of MDB-like symptoms in childhood, family history of epilepsy, non-paroxysmal psychopathology, and personality traits; 2) Electroencephalographic data obtained from both a baseline and a chloralose activated record and coded on a complete set of EEG abnormalities. **Results:** Analysis of the EEG data shows no significant abnormalities in patients with IED; actually, hypersynchrony is significantly more common in the control group. IED patients report a great deal of anger, rage and violence, smash things, attack and hurt others. Anger is also displayed in other behaviors such as driving a car recklessly. Subjectively they report often feeling like hurting others, feeling angry enough to kill and worrying about losing control. Others are reported frightened by their anger. They also report fits of anxiety and depression, autonomic episodes, impulsivity, hypochondriac symtpoms, disturbed sleep, phobias, and a history of adolescent behavior problems and delinquency much more frequently than the control group. These differences are at the 0.00 level of significance. **Conclusion:** the findings do not support DSM-III diagnostic criteria for IED but rather suggests it to be a disorder characterized by personality traits of anger, aggresiveness and impulsivity and a more pervasive psychopathology including behavior problems and delinquency in adolescence and the presence of more general psychopathological manifestations.

NR101 Wednesday, May 9, 12 Noon-2:00 P.M.

CARBAMAZEPINE VERSUS PROPRANOLOL FOR RAGE OUTBURSTS

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Summary:

Both PPL and CMZ have been reported to be helpful in patients with rage outbursts;this study sought predictors of differential benefit. Subjects met the first two DSM-III criteria for Intermittent Explosive Disorder(IED):(1)Several discrete episodes of loss of control of aggressive impulses resulting in serious assault or destruction of property,and(2)Behavior that is grossly out of proportion to any precipitating psychosocial stressor. Treatment: Subjects were randomly assigned to CMZ or PPL. Given clinical concerns, since a 3-6 month out-patient follow-up was deemed necessary to evaluate drug response, drugs were not given "blind."

Evaluation: To identify potential predictors of response,the following variables were evaluated:(1)Diagnosis(2)CAT Scan(3)Sleep EEG with nasopharyngeal leads (4)neuropsych testing and (5)clinical ratings including severity and frequency of outbursts,prodromal signs,amnesia for episode,and role of alcohol in precipitating episodes. Non-blind ratings at discharge and follow-up were performed by psychiatrist,patient and "significant other"; similar ratings were performed by a research assistant blind to drug status. Results are preliminary; 46 patients have entered,but not all analyses have been done to date(1/26/84). Most will be done by the APA and will be presented. About 30% of patients had Attention Deficit Disorder, Residual type,40% had IED, 15% had Antisocial Personalities and 35% had a neurological disorder (eg.,known brain damage). Approximately 40% had abnormal EEG's and 35% had abnormal neuropsych testing.

Two-way analyses were performed with medication(CMZ vs PPL) on one axis and patient characteristic or diagnosis on the other axis. Separate analyses were performed for each patient characteristic(e.g. EEG, role of alcohol,etc). Most patients improved on either medication, but no diagnosis nor other patient characteristic predicted response to either medication. While provisional,these results suggest both drugs increase the threshhold for aggression regardless of the cause for outbursts. A biochemical similarity between the drugs might be responsible for this effect.

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PREMENSTRUAL MOOD DISORDER AND PSYCHIATRIC ILLNESS

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Summary:

Previous studies suggesting a relationship between psychiatric illness (principally affective disorder) and menstrually related mood disorders have relied exclusively on retrospective techniques to establish the existence of the latter disorder. While retrospective diagnoses of major psychiatric disorders via The Schedule for Affective Disorders and Schizophrenia-Lifetime (SADS-L) have been shown to be valid and reliable, retrospective diagnoses of menstrually related mood disorders are not and hence require prospective confirmation. We evaluated 60 women self referred for "premenstrual syndrome" who retrospectively reported the occurence of significant affective symptoms confined to the premenstrual time period. Prospective assessment over three menstrual cycles using visual analogue mood scales indicated that only 28 of 60 (47%) patients demonstrated a significant ($\geq$ 30%) increase in mood symptoms in the week prior to menses compared with the week following menses. The other group of patients had only mild premenstrual symptom increase ($\leq$ 10%), frequent mood changes throughout the cycle, or chronic symptoms of depression and/or anxiety. Lifetime diagnoses were assessed in the two groups using the SADS-L modified so as to eliminate from consideration disorders believed to be entirely confined to the premenstruum. The group that failed to have menstrually related mood disorder prospectively confirmed were significantly more likely to meet criteria for an RDC defined psychiatric disorder than were the group with menstrually related mood disorders ($x^2 = 7.46$, $p < .01$) despite elimination of the premenstrual time period from diagnostic consideration. The clinical and theoretical implications of these findings and their relation to previous studies will be discussed.

NR103 Wednesday, May 9, 12 Noon-2:00 P.M.

DOUBLE-BLIND TRIAL OF THIOTHIXENE IN BORDERLINES

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Summary:

Introduction: Explicit criteria for the diagnosis of borderline and schizotypal personality disorders have made biological and pharmacological studies possible. In recent examinations of this biological facet of borderline personality disorder, investigators have noted abnormal DSTs and TRH tests, shortened REM latency, and an abnormal sensitivity to amphetamine. Studies of schizotypal patients have shown abnormal responses in eye-tracking and attention testing. The pharmacological approach to these two frequently overlapping disorders began with Klein's work showing improvement of pseudoneurotic schizophrenics following imipramine and of emotionally unstable character disorders following chlorpromazine treatment. The concept of low-dose neuroleptic treatment was introduced by Brinkley, Beitman, and Friedel in 1979 with a series of case descriptions that led to renewed interest in antipsychotic medication. The present study examines the response of borderline and schizotypal patients to low-dose thiothixene in a double-blind placebo-controlled trial. Methods: Fifty outpatients between the ages of 18 and 55 who satisfied DSM-III criteria for borderline and/or schizotypal personality disorder were included. Diagnosis was made using the Schedule for Interviewing Borderlines (Baron et al). Patients were randomly assigned to thiothixene (starting dose 5 mg) or placebo. These patients were rated using a modification of the SIB, the GAS, and the HSCL-90 weekly for 4 weeks and then bi-weekly up to 12 weeks. Results: Global Assessment Scale scores showed significant improvement in both groups. Interestingly, even though global improvement was similar for both groups, there were significant advantages for the thiothixene treated group in a number of symptom clusters when the data were analyzed using one-way analysis of covariance. The thiothixene group had significantly greater improvement on HSCL-90 psychotic score, illusions, ideas of reference, and phobic anxiety. The mean dose of thiothixene was 8.67 mg compared to a 26.4 mg dose for the placebo group. Discussion: This is the first controlled study that demonstrates the efficacy of the low-dose neuroleptic strategy in borderline/schizotypal patients. The results indicate that not all patients in these diagnostic groups benefit from medication, but that those with relatively high scores on the above mentioned scales improve significantly more when taking thiothixene rather than placebo.

NR104 Wednesday, May 9, 12 Noon-2:00 P.M.

BORDERLINE PERSONALITY DISORDER: 14 YEAR OUTCOME

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Stockbridge, MA

Summary:

To explore long-term outcome of borderline personality disorder (BPD) and the significance of its frequent overlap with schizotypal personality disorder (SPD), we studied admission and mean 14 year follow-up functioning as measured by the Global Assessment Scale in 63 inpatients meeting DSM-III criteria for BPD alone or in combination with SPD, schizoid personality disorder (SDPD) or major affective disorder (MAD), and compared them to patients with schizophrenic disorder or MAD, SPD or SDPD alone.

At admission and follow-up patients with MAD were functioning better than schizophrenics. BPD patients free of MAD functioned better at admission and follow-up than schizophrenics but were indistinguishable from patients with MAD. This lends further credence to the view of BPD as fundamentally different from schizophrenia. We find no evidence of a fundamental difference between BPD and MAD, but the lack of a fundamental difference cannot be equated with a similarity between them. BPD with SPD patients were as impaired at admission as schizophrenics, but at follow-up were functioning significantly better than schizophrenics and possibly better than patients with MAD or BPD. This is a previously unreported finding of significant interest, especially in light of the frequent overlap reported between BPD and SPD. Finally, the presence of MAD in patients with BPD did not predict better functioning than BPD without MAD at admission or follow-up despite a previous report to that effect by Pope et al (Arch Gen Psych, 1982). Our findings tend to agree with and extend those reported by McGlashan (Arch Gen Psych, 1982) and to disagree with those of Pope et al. We explore possible explanations for the discrepancies between studies, including pharmacologic and psychotherapeutic treatment effects. We raise the question of whether BPD with SPD is a disorder especially appropriate for long-term intensive psychotherapy or whether it represents a "good prognosis personality disorder." We explore which criteria of BPD and SPD were the best predictors of good outcome.

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NEUROLOGICAL FINDINGS IN ADULTS WITH HISTORY OF MINIMAL BRAIN DYSFUNCTION

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Summary:

Minimal Brain Dysfunction(MBD) is a disorder characterized by inattention, hyperactivity, impulsivity, and evidence of subtle brain dysfunction, with an onset in early childhood. Although attention has been given to the persistence of behavioral symptoms into adulthood, little is known of the neurological basis of this condition. This study was undertaken to examine CNS structure and function in a group of patients with a childhood diagnosis of MBD.

A group of young males, ages 21-26(N=23), who were hospitalized on the University of Iowa Child Psychiatry ward between the ages of five and seven with a diagnosis of MBD was studied with a battery of neurological tests and compared with a control population of age- and sex-matched hospital workers(N=29). None were taking psychotropic medication at the time of the study. The testing consisted of (1)a neurological soft signs(NSS) battery of motor, sensory, and cognitive tests designed to screen for brain dysfunction, (2)a sensory-motor laterality battery, and (3)a Picker brain CT scan. The MBD patients were compared to psychiatric patients with diagnoses of chronic schizophrenia(N=44) and bipolar affective disorder(N=28) who were given the same NSS and laterality tests in a previous study. CT scans were read blindly and measures were obtained of the ventricle/brain ratio(VBR) of the lateral and 3rd ventricles, as well as sulcal widening and cerebellar atrophy.

MBD patients differed from controls on 11 of 30 subtests of the NSS battery at the $p<.05$ level or better(chi square or Fisher's exact test). Items most strongly differentiating MBD patients from controls were 2-dimensional constructional praxis($p<.001$), left-right orientation($p<.001$), crossed replication of hand position($p<.01$), and fine motor movements($p<.05$). Five of the MBD patients(20.8%) were left-handed--they did not differ from the right handed patients on the NSS measures. Abnormalities on the NSS tests were not associated with lateral or 3rd ventricle enlargement, sulcal widening(13/23 patients, 56.5%), or cerebellar atrophy(6/23 patients, 26.1%).

Results of the NSS and laterality tests will be contrasted to the findings in the schizophrenic and bipolar psychiatric patient groups. Implications and directions for future research in the neurological aspects of MBD will be discussed.

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THE PERSONALITY DISORDER EXAMINATION (PDE)

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Summary:

DSM-III marked a major development in the history of the classification of personality disorders, because it was the first nosological system to provide explicit, detailed and potentially reproducible diagnostic criteria. However, the reliability data from the field trials were disappointing. The manual states: "the kappas for the specific Personality Disorders are quite low and range from 0.26 to 0.75." The reliability of Axis II diagnoses might be enhanced by the availability of a structured interview, which would allow the clinician or research investigator to conduct a systematic examination for the presence or absence of the various criteria used to make the diagnosis of the individual personality disorders. But the three most widely used structured interviews in psychiatry, the Present State Examination (PSE), Schedule for Affective Disorders and Schizophrenia (SADS), and Diagnostic Interview Schedule (DIS), do not provide sufficient coverage of the clinical phenomena associated with most Axis II diagnoses. Therefore, we developed the Personality Disorder Examination (PDE), which systematically surveys the phenomenology and life experiences that are required to diagnose all eleven personality disorders. The format resembles a clinical interview more than a questionnaire, and is designed to maintain rapport and encourage valid replies from the subject. The questions flow in a natural sequence, but do not violate the requirements of standardization and objectivity. They are organized around central themes concerning work functioning, identity or sense of self, interpersonal relationships, affects, reality testing, and impulse control. There are approximately 300 items, including some about the subject's behavior during the interview itself. Several questions sample each of the individual criteria for the various personality disorders. Although the items are scored by the examiner, algorithms permit the clerical assignment of DSM-III Axis II diagnoses. The scores on all of the items sampling a particular personality disorder can be summed, so that every subject also has a dimensional score on each of the eleven disorders. Interrater agreement was determined on a sample of 30 patients with suspected personality disorders. The r's (intraclass correlation coefficients)for DSM-III diagnoses ranged from .68 (Avoidant) to .92 (Histrionic) with a median of .83, and for dimensional scores from .86 (Narcissistic) to .98 (Borderline) with a median of .96.

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MITRAL VALVE DISEASE IN ANXIOUS PATIENTS

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Summary:

Sixty-four subjects attending a research clinic underwent echocardiogram (ECHO) evaluation to determine the presence of mitral valve prolapse (MVP) or valvular disease. Patients met DSM III criteria for generalized anxiety disorder (GAD), panic disorder (PD), or agoraphobia with panic attacks; a subgroup was diagnosed as having atypical panic disorder - meeting criteria for GAD, but also found to have panic attacks of insufficient frequency to diagnose panic disorder. ECHO's were interpreted by an echocardiologist blinded to the patients' psychiatric diagnosis. Cardiac diagnosis was based on 2-dimensional (2-D) and M-mode echo recordings, with a scale of graduated strictness of criteria used for diagnosis. Thus, the most stringent criteria used were 2-D evidence of prolapse on the apical 4 chamber and parasternal long axis views or prolapse on one 2-D view with U-mode confirmation, while a less stringent criteria used was evidence of prolapse on one 2-D view. Also diagnosed was the incident of significant myxomatous changes in conjunction with flat closure of the mitral valve, but insufficient buckling to diagnose prolapse (valvular ds).

Results showed an increased incidence of mitral valve disease for patients with panic attacks as compared to strictly defined GAD patients, dependent upon criteria used to diagnose valvular disease. These data strengthen the notion of a relationship between cardiac disease and the phenomena of panic attack. These findings will be discussed and compare with prior cardiac studies of anxiety patients from other centers.

Dx	MVP (2 views)	MVP (1 or 2) views	Valvular ds	Normal	Total
GAD	3 (15%)	6 (30%)	6 (30%)	14	20
PD	8 (33%)	10 (42%)	14 (58%)	10	24
Agoraphobia c PAs	4 (36%)	5 (45%)	6 (54%)	5	11
Atypical PD	3 (33%)	4 (44%)	6 (67%)	3	9

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NOREPINEPHRINE IN POST-TRAUMATIC STRESS DISORDER

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Summary:

Because high levels of norepinephrine (NE) have been found among depressed patients with concurrent anxiety, we hypothesized that depressed patients with post traumatic stress disorder (PTSD) would have higher levels of 24-hour urinary NE than other patients with major depressive disorders (MDD). Trained clinicians used the Research Diagnostic Criteria for major or minor depression and the DSM III for PTSD. Nine males with PTSD and depression (five with MDD), and 10 males with MDD alone were hospitalized for 5 to 12 weeks with 24-hour urines collected biweekly. For the total hospitalization, the PTSD patients had higher mean NE levels than the MDD patients (76 vs. 46.5 µg/24 hrs, $t=2.4$, d.f.=17, $p<0.05$). The five PTSD patients with MDD had a mean NE level of 65 µg/24 hrs. Because the MDD group was older (49 vs. 38 yrs, $t=2.3$, d.f.=17, $p<0.05$), we adjusted for age using ANCOVA. This adjustment increased the significance of the NE difference ($F(1,17)=9.4$, $p<0.01$). Because four PTSD and seven MDD were started on antidepressants (ADep) during hospitalization, the initial drug-free NE levels were age adjusted and compared. The drug-free NE levels were higher for PTSD (73 µg/24 hrs) than for MDD (47 µg/24 hrs) ($F(1,15)=7.4$, $p<0.05$). Additionally, the total hospitalization NE levels were adjusted for medications using a two-way ANOVA, and only the diagnostic group effect was significant ($F(1,15)=6.2$, $p<0.05$) with the ADep free patients having NE levels of 95.1 µg/24 hrs for PTSD vs. 44 µg/24 hrs for MDD. We concluded that males with both depression and PTSD can be biologically distinguished for MDD alone by unusually high levels of sympathetic nervous system (SNS) activity, as indicated by higher NE levels. This finding is consistent with other studies of PTSD using indirect measures of SNS activity. ADep treatment may decrease these high NE levels and aid recovery from PTSD.

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IN SEARCH OF BIOLOGICAL MARKERS FOR ANXIETY

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Summary:

In contrast to affective disorders, there has not yet been much investigation into the possible existence of biological markers in anxiety states. Our purposes in searching for such markers have been (1) to further elucidate the emerging body of knowledge concerning the biochemistry of anxiety and (2) to bring added objectivity into the evaluation of anxiety. Our first study has been designed to determine whether or not there is a positive correlation between the presence of acute (state) anxiety and elevated serum "liver" enzymes, specifically, (1) serum glutamic oxalo-acetic transaminase (SGOT), (2) serum glutamic phosphoric transaminase (SGPT), and (3) lactate dehydrogenase (LDH). This study has been based on the biochemistry of gamma amino butyric acid (GABA), one of three neurotransmitters which has been recently implicated in the genesis of anxiety. Several investigations have demonstrated that elevated anxiety levels have been associated with decreased or depleted serum GABA; hence, our conjecture that in certain anxious individuals, decreased serum GABA might lead to increased SGOT, SGPT, or LDH activity in the liver and in the brain to homeostatically restore normal GABA levels in serum and tissue, as a means of diminishing anxiety. Results thus far have been encouraging. Ten (10) of the first twenty-five (25) subjects or 40% of our test group have had at least one elevated liver enzyme correlating positively with anxiety levels from mild to severe on both the SCL-90 Anxiety Checklist and on their psychiatrist's ratings, even though there have been some significant disagreements between the two sets of ratings. Nine (9) of the ten (10) have shown elevations in only one liver enzyme, either LDH (6) or SGPT (3), never SGOT (0). The tenth subject showed abnormally increased levels in all three enzymes. In eight out of ten patients, the elevated liver enzymes decreased as did their anxiety ratings after one week. In the two patients whose liver enzymes increased beyond the normal range after one week, both rated their anxiety levels to be lower but the psychiatrist ratings split, one higher and one lower. We view the results thus far as supportive of our hypothesis that increased LDH, SGPT, or SGOT activity may reflect a homeostatic attempt to increase brain GABA as a biochemical means of diminishing anxiety. If future results continue to demonstrate this positive correlation, it could mean that certain easily accessible serum "liver" enzymes, particularly LDH and SGPT, might be viewed as biological markers for anxiety.

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THE CENTER FOR EPIDEMIOLOGIC STUDIES DEPRESSION SCALE: REPORT ON ITS VALIDITY WITH MAJOR DEPRESSION AND GENERALIZED ANXIETY

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Summary:

The Center for Epidemiologic Studies Depression Scale (CES-D) has been the most widely used measure of depressive symptoms in epidemiology. Previous studies examined its relationship to clinical depression by comparing scores on the scale with data from validated diagnostic instruments. While the CES-D was found to have discriminant validity for depression, when contrasted with drug addiction, alcoholism, or schizophrenia, it is important that it also discriminate depression from generalized anxiety, a diagnostic category with overlapping symptomatology with depression.

This study evaluates the validity of the CES-D by comparing it to DSM III diagnoses of major depression and generalized anxiety, using the NIMH Diagnostic Interview Schedule (DIS). Data were gathered on a sample of 310 mothers of children with chronic disabilities. The findings indicate that the utility of the CES-D (in terms of its sensitivity and specificity) for detecting major depression was approximately equal to its utility for detecting generalized anxiety. Specificity was 73% for both disorders and sensitivity was 87.5% and 80% for major depression and generalized anxiety, respectively. Multivariate analysis revealed that the unique association of CES-D with current depression was equal to its association with current generalized anxiety and that each of the two disorders had an independent and additive effect on CES-D. Thus persons with current diagnosis of both disorders scored, on the average, markedly higher than persons with only one current disorder (mean of persons with both disorders was 37, of those with major depression alone, 20 and with generalized anxiety alone, 23). The association of CES-D with past generalized anxiety was stronger than with past major depression. Examination of individual CES-D symptoms did not identify any symptom as specific to either one or the other disorder. The findings, therefore, do not support the notion that the CES-D scale measures depression specifically.

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URINARY CATECHOLAMINES IN PANIC ANXIETY PATIENTS

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Summary:

Urinary and plasma catecholamine (CA) elevations have been associated with stress and anxiety. Mitral valve prolapse (MVP) has also been associated with increased autonomic activity and CA elevations as well as the specific DSM-III-defined anxiety syndrome-panic disorder. In this study two consecutive 12-hour urinary aliquots (7a.m.-7p.m.,7p.m.-7a.m.) collected during normal activity from 23 drug-free patients with panic attacks and 9 normal controls, were analyzed for free norepinephrine (N) and epinephrine (E) (mcg/12-hour collection). In comparison to normals, patients showed significant elevations of both CA in the evening aliquots (N:16.38 vs 8.96; E:6.52 vs 4.14), and N (21.48 vs 13.84) in the daytime specimen. The normal circadian reduction of both CA in the evening was observed in both patients (N:21.48 vs 16.38; E:8.53 vs 6.52) and normals (N:13.84 vs 9.96; E:7.09 vs 4.14). Twenty of 23 patients had evaluations for MVP, including 2-D and M-mode echocardiography, phonocardiography, and auscultation; 7 were positive (35%). Both CA from the 13 patients without MVP (N:19.48; E:7.88) were significantly greater than from the 7 with MVP (N:10.94; E:4.47) in the evening specimens. Nine patients (3 with MVP) were restudied after treatment. Both evening CA showed partial reductions toward normal (N:15.69 to 10.85; E:5.78 to 4.63), significant for N but not E. This study supports prior research in which plasma CA were elevated in panic patients, and suggests that there may be differences in adrenergic tone in panic patients with versus without MVP. Both pre-treatment differences and treatment changes were greater in the evening specimens. Although not designed for this purpose, these results support prior findings of increased incidence of MVP in people with panic attacks.

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VALIDITY OF SELF-REPORTED ANXIETY SYMPTOMS

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Summary:

In patients with anxiety disorder, evaluation of somatic symptoms assessment and of their change depends to a large extent on patients' self-reports. To investigate the validity of such reports, eighteen outpatients diagnosed as having generalized anxiety disorder were rated on the Hamilton Anxiety Scale (HAM-A) and rated themselves on the Somatic Symptom Scale (SSS) and on analogue scales (sweating, palpitations, shaking, muscular tension). Patients then underwent a psychophysiologic examination which included muscle activity (forehead and gastrocnemius EMG), heart rate (interbeat interval, IBI) and sweat gland activity (skin conductance). Recordings were obtained during rest (baseline) and during a stress task (Stroop Test). All scales correlated significantly on global scores; on subscales, however, only scales describing cardiac symptoms correlated well (HAM-A : SSS $r=.78$, $p<.005$).

All cardiac subscales correlated well with the average IBI (HAM-A: $r= -.51$, $p<.025$; SSS: $r=.42$, $p<.05$; analogue scale: $r=.57$, $p<.01$). None of the other scales correlated with physiological measures. During the stress task, the analogue scale, "palpitations," correlated with the IBI range ($r=.52$, $p<.025$) and the analogue scale, "muscle tension," with the gastrocnemius EMG ($r=.49$, $p<.025$). From baseline to the end of the stress task, analogue ratings increased for sweating, shaking ($p<.05$ for both), and marginally for palpitations ($p<.10$), but not for muscle tension. Actual physiological measures revealed that skin conductance (fluctuations and tonic level) increased, IBI decreased, and gastrocnemius activity (EMG) increased significantly ($p<.005$ for all). In summary, during rest, self-ratings of cardiac symptoms were good indicators of heart rate; other self-ratings did not correlate with patients' physiologic state. Under stress, averaged self-ratings and averaged autonomic responses changed in the same direction. While this finding is valid at the group level, only heart rate reflected reliably the physiologic state and its change during stress in individual ratings.

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NORTRIPTYLINE VERSUS PSYCHOTHERAPY IN DEPRESSED ELDERLY

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Summary:

This is a double-blind study to compare the effectiveness of interpersonal psychotherapy (IPT) with nortriptyline (NT) and a placebo control group in the treatment of moderately depressed geriatric outpatients. Subjects are 60 years of age or older, ambulatory, able to come weekly to the clinic, meet RDC criteria for major depressive disorder, score at least 17 on the Hamilton Depression Rating Scale (HDRS), and at least 15 on the Beck Depression Inventory. Subjects are randomly assigned to one of three groups and treated for 16 weeks. The NT group was started at 25mg per day rising to 125mg in some patients sufficient to reach the therapeutic window. The placebo group was given identically appearing capsules and treated similarly. IPT subjects were seen weekly for 50 minutes.

Preliminary results from the first six weeks of treatment are presented for 51 subjects, 23 male and 28 female. Fifteen subjects completed IPT; 11 completed NT; and 12 completed placebo. Both NT and IPT gave essentially equal improvement based on HDRS and other scores. However there were more dropouts from the NT treated group. Seven failed to complete six weeks--most because of side effects. The dropout rates of the IPT and placebo groups were much less and comparable with each other. Of the placebo group only one improved significantly after six weeks. Plasma levels were also correlated with improvement and side effects. This is a continuing study and more data analysis will be available.

NR114 Wednesday, May 9, 12 Noon-2:00 P.M.

CHILDHOOD PREDICTORS OF ADULT SCHIZOPHRENIA

Ernest Hartmann, M.D., Sleep Research Laboratory, Lemuel Shattuck Hospital, 170 Morton Street, Boston, MA 02130, Eva Milofsky, M.S.W. (I), George E. Vaillant, M.D., Molly Oldfield, Ed.M. (I), Roberta Falke, B.A. (I), Charles Ducey, Ph.D. (I), Patricia Brune, B.A. (I), Daniel Greenwald, B.A. (I), Walter Mitchell, Psy.D (I), Boston, MA

Summary:

Data from two large groups of children seen in the 1940s and followed up as adults were employed to assess the ability of a group of "Indicators of Vulnerability" to predict adult schizophrenia. The first data base consisted of the 1,000 children studied by Glueck and Glueck in 1945 and followed up several times through the 1970s. Twenty-four had received a hospital diagnosis of adult schizophrenia. These 24 were matched with 48 others in whom the outcome was nonschizophrenic and nonschizophrenic spectrum. The childhood data of these 72 cases were scored on a blind basis. The second study involved data from children seen at the Judge Baker Child Guidance Center in the 1940s with follow up data available in the late 1960s. In this study, 32 with an outcome of adult schizophrenia (hospital diagnosis) were matched with 33 with a "normal" outcome and 35 in whom the outcome was "character disorder" severe enough to require hospitalization. The 100 childhood records were scored by raters unaware of the outcome.

Inter-rater correlation coefficients were approximately 0.7. In the first study, the mean total scores of two raters on our a priori scoring instrument, "Indicators of Vulnerability," separated the schizophrenic-outcome from the nonschizophrenic-outcome group as follows: Sc Group: 33.0 $\pm$ 8.3; Non-Sc Group: 25.8 $\pm$ 7.8; t=3.7, $p < .001$. In the second study, the schizophrenic group was separated from the two other groups on a similar total score as follows: Sc Group: 24.0 $\pm$ 7.8; Normal: 15.3 $\pm$ 5.1; Character Disorder: 15.9 $\pm$ 5.4; F (2, 97) = 20.0, $p < .001$; Sc > N, CD (t-tests) $p < .001$. The individual "Indicators of Vulnerability" (named Unusual Anxiety, Neophobia, Lack of Historicity, Inappropriate Affect, Anhedonia, Lack of Object Constancy, Permeable Boundaries, Lack of Competency, Difficulties in Interpersonal Relationships, Chemical and Neurological Abnormalities, Inappropriate Anger and Aggression) were able to separate the outcome groups as well. The "poor outcome control group" (Character Disorder) scored similarly to the normal outcome group and differently from the schizophrenic outcome group on almost all measures.

NR115 Wednesday, May 9, 12 Noon-2:00 P.M.

ORAL PHYSOSTIGMINE TREATMENT OF PATIENTS WITH ALZHEIMER'S DISEASE

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Summary:

Neurochemical studies have demonstrated convincingly that patients with Alzheimer's disease or senile dementia of the Alzheimer type (AD/SDAT) have a dramatic loss of cholinergic cells in brain. Attempts to treat AD/SDAT with precursors to acetylcholine have not been successful because these substances do not increase cholinergic activity. When given intravenously in an appropriate dose, the cholinesterase inhibitor physostigmine, has been shown to transiently improve memory in patients with AD/SDAT (e.g. Christie et al, Br. J. Psychiat. 1981, 138:46-50; Davis and Mohs, Am. J. Psychiat. 1982, 139: 1421-1424). The present study assessed the overall clinical efficacy of chornic oral physostigmine treatment in 12 patients with clinically diagnosed AD/SDAT. In an initial dose-finding phase patients received 0.0, 0.5, 1.0, 1.5, and 2.0 mg of physostigmine Q2H during waking hours for 3-5 days. Symptoms, including memory impairment, dysphasia, dyspraxia, agitation and mood disturbance were assessed with the Alzheimer's Disease Assessment Scale (ADAS) on the last day at each dose. In a subsequent replication phase, placebo and the dose associated with the least severe symptoms were readministered for 3-5 days each. Since it was expected that the effects of oral physostigmine on central cholinergic activity would vary among individuals, a more direct biological indicator of cholinergic activity was sought. On the last night of placebo and physostigmine treatment blood was drawn every 30 min. for measurement of plasma cortisol since central cholinergic stimulation raises plasma cortisol levels. One patient's symptoms did not improve on any dose of physostigmine in the dose-finding phase and another became too uncooperative to complete the study. Of the remaining 10 patients, 3 had clinically significant improvement on the highest dose of physostigmine in both phases, 4 more were marginally improved in both phases and 3 had inconsistent responses to physostigmine. A rank order correlation indicated a significant positive relationship between percent decrease in symptoms on the ADAS due to physostigmine and percent increase in mean cortisol due to physostigmine (Tau = .57, $p < .03$). Thus, physostigmine is likely to improve symptoms only in a subgroup of patient in whom the drug actually enhances central cholinergic activity.

NR116 Wednesday, May 9, 12 Noon-2:00 P.M.

DEPRESSION AND THE CAPACITY TO GIVE INFORMED CONSENT

Barbara Stanley, Ph.D. (I), Lafayette Clinic, 951 E. Lafayette, Detroit, MI 48207; Eric D. Peselow, M.D., Brooklyn, NY; Michael Stanley, Ph.D. (I), Detroit, MI; Faouzia Barouche, M.D. (I), Ronald R. Fieve, M.D., New York, NY

Summary:

A prerequisite to conducting research in human subjects is obtaining informed consent. It is felt by many that patients with major psychiatric disorders have impaired ability to give informed consent. Indeed, research on psychiatric subjects is often done when the patient has active psychopathology. For instance, many depressed patients are felt to have disturbances in their cognitive ability which may alter their ability to interpret information.

We attempted to evaluate whether depressed patients had any difference in their ability to perceive research procedures as compared with normal controls. To date, we have evaluated 77 people who have undergone an actual research procedure- the dexamethasone suppression test. This group included 28 patients with active major depressive disease as defined by RDC, 21 patients with a lifetime history of depression who were not currently depressed, and 28 normal controls. Prior to receiving the DST, all participants signed a consent form which was read to them by an investigator. The consent form contained information concerning the method, purpose, benefit, and risk of the DST. Following this explanation, the participants were asked to write down their understanding of the method, purpose, benefit, and risk of the DST, as well as their for participating and their interest in doing so. Their responses were scored by raters blind to diagnosis. Prior to receiving the DST, all participants (patients and controls) were rated with a Hamilton and Beck depression scales and were given an IQ test.

The results of the study indicate that the presence of depression or the diagnosis of major affective disorder did not interfere with the ability of the participant to give informed consent. Neither depressive symptoms as measured by the above scales, diagnostic category, interest, or IQ had any correlation with participation in the study, and these parameters did not correlate with greater understanding of the purpose, benefit, method, & risk of the DST.

NR117 Wednesday, May 9, 12 Noon-2:00 P.M.

ARE SUBTYPES OF DEPRESSION RELATED TO PERSONALITY?

Bruce Pfohl, M.D., University of Iowa, Department of Psychiatry, 500 Newton Road, Iowa City, IA 52242, Camille Logue, Ph.D. (I), Dalene Stangl, M.A. (I), Iowa City, IA

Summary:

We studied a consecutive series of 78 patients who were admitted to the University of Iowa and met DSM-III criteria for major depression without psychotic symptoms. Patients were given the Structured Interview for DSM-III Personality Disorders (SIDP) which involved an extensive interview of both the patient and a knowledgeable informant.

Forty-one (52%) of the 78 depressed patients also met criteria for at least one DSM-III personality disorder (PD) with borderline, histrionic and dependent personalities occurring most frequently. The PD patients had significantly higher Hamilton and Beck depression scores at the time of admission and were significantly less likely to have a 50% drop in scores by the time of discharge. The PD patients were 3 times as likely to have made medically nonserious suicide attempts than no-PD patients (39% vs. 11%) yet both groups made medically serious suicide attempts at the same rate (5%).

Morbidity risk for alcoholism among first degree family members of the PD patients was 18% compared to 5% for relatives of no-PD patients. Twenty percent of the depressed patients with PD were DST nonsuppressors compared to 43% of no-PD patients. Neither the RDC endogenous criteria nor the DSM-III melancholia criteria significantly distinguished between the two groups however by the Newcastle rating score the no-PD group scored significantly higher in the endogenous direction. Comparing individual DSM-III personality disorders revealed relatively few significant differences although the PD patients with multiple PD diagnosis covering more than one DSM-III cluster looked more pathologic on a varietv of measures than did patients with PD from only one cluster.

Personality disorder may frequently coexist with DSM-III major depression. The combination appears to be associated with a different family history, a different pattern of symptoms and a worse response to treatment when compared to major depression alone. The precise etiologic relationship between depression and PD is far from clear.

NR118 Wednesday, May 9, 12 Noon-2:00 P.M.

ESTROGEN REPLACEMENT AND TARDIVE DYSKINESIA

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Summary:

Tardive dyskinesia (TD) is an involuntary movement disorder that is thought to be due to supersensitivity of nigrostriatal dopamine receptors induced by the chronic administration of neuroleptic medication. Since older female patients have been reported to be at greater risk for developing TD, and since there are uncontrolled reports of improvement of TD after estrogen replacement in older women, we conducted a controlled study to see if Estrogen Replacement therapy (ERT) could improve TD in a postmenopausal female population.

Twelve postmenopausal women with TD on neuroleptic medications were selected from the Tardive Dyskinesia Clinic at the Connecticut Mental Health Center in New Haven, Connecticut. They were randomly assigned to ERT (Premarin 1.25 mg tablets per day) or placebo. Patients were seen once a week by two blind raters who administered the Abnormal Involuntary Movement Scale(AIMS), the Brief Psychiatry Rating Scale (BPRS) and the Webster Scale for parkinsonian signs. On the first and last visit, a gynecologist, also blind to treatment assignment obtained a PAP smear for vaginal and cervical cytology and maturational index as well as serum estradiol and prolactin samples. Seperate video recordings were made on the first and last visit. Interrater agreement on all scales were acceptable.

Ten of the twelve patients completed the study leaving five patients receiving ERT and five receiving placebo. Using the Mann Whitney U test to compare changes in AIMS scores between the two treatment groups at each visit, we found a significant ($p=.048$) effect of ERT after three weeks exposure. All ERT patients showed a range of improvement in their AIMS scores between visits one and four from 17% to 50% (average improvement 37% per patient). There was no statistical difference between treatment groups for parkinsonian signs, frequency counts of the most severe involuntary movement or total BPRS scores. There were no adverse reactions related to ERT.

These data have obvious applicability to the treatment and/or prevention of TD. In addition, these data add to a growing interest in the area of central nervous system - hormone interaction, specifically, the relationship of estrogen to striatal dopamine function. Our discussion will include an attempt to relate our results to recent animal studies.

NR119 Wednesday, May 9, 12 Noon-2:00 P.M.

PLATELET MAO IN DEPRESSION WITH REVERSIBLE DEMENTIA

George S. Alexopoulos, M.D., New York Hospital-Cornell Medical Center, Westchester Division, 21 Bloomingdale Road, White Plains, NY 10605, K.W. Lieberman, M.D. (I), R.C. Young, M.D., C.A. Shamoian, M.D., White Plains, NY

Summary:

Some elderly depressives develop a dementia syndrome which improves significantly when depression improves. We hypothesized that this reversible dementia (DRD) develops in patients with subclinical Alzheimer's disease process when pathophysiological changes of depression are superimposed. To test this hypothesis we studied platelet monoamine oxidase (MAO) activity in a large population of hospitalized geriatric patients. MAO is an enzyme which catabolizes catecholamines and serotonin and platelet MAO activity has been used as an index of brain monoaminergic activity. We have recently reported that patients with primary degenerative dementia have significantly higher platelet MAO activity than normal controls, while elderly depressives have values indistinguishable from those of same age normal subjects.

Eighty-four depressed geriatric inpatients were studied. DSM III and Research Diagnostic Criteria were used to make the diagnosis and syndrome classification. Symptoms of depression were rated with the 24-item Hamilton Depression Rating Scale (HDRS) and cognitive impairment with the Minimental State (MMS). When sampled, subjects were not on drugs known to influence platelet MAO activity. Platelet MAO activity was assayed with benzylamine as the substrate and values were expressed in nmol/mg protein/hour. Patients with major depression and dementia whose affective (ΔHDRS $\geq$ 10 or final HDRS $\leq$ 12) and cognitive symptoms improved (more than 3 points in MMS) and reached a MMS of 24 or greater were classified as DRD. Fourteen patients with depression and dementia had no cognitive change after improvement of depression (ΔHDRS $\geq$ 10 or final HDRS $\leq$ 12) and met criteria for primary degenerative dementia (DD). Platelet MAO activity was significantly different between cognitively intact major depressives (N=47), DRD patients (N=23) and DD patients (N=14) (one way ANOVA, $F=14.05$, $d=2,81$, $p < 0.001$). Post hoc comparison of means showed that DRD ($\bar{x}=69.3$, SE=5.0) and DD patients ($\bar{x}=80.5$, SE=4.7) had significantly higher platelet MAO activity than cognitively intact depressives ($\bar{x}=50.3$, SE=2.9) but their values were indistinguishable from each other. Since gender may influence platelet MAO activity, women were analyzed separately. Again, significant differences in platelet MAO activity were found between cognitively intact depressives (N=37), DRD (N=20), and DD patients (N=13), ($F=10.15$, df=2, 67, $p < 0.001$). Platelet MAO activity was similar in women with DRD ($x=69.0$, SE=5.4) and DD ($\bar{x}=78.6$, SE=4.6). These values were significantly higher than those of cognitively intact depressed women ($\bar{x}=50.8$, SE=3.4).

Since DRD patients had as high platelet MAO activity as DD and our previously reported patients with primary degenerative dementia, we conclude that the data are consistent with our hypothesis.

NR120 Wednesday, May 9, 12 Noon-2:00 P.M.

PSYCHOLOGICAL AND ENDOCRINE EVALUATION OF BULIMIA

Enrique J. Friedman, M.D., 1321 N. Harbor Boulevard, Fullerton, CA 92635, Marc Stolar, M.D. (1) Meagan Kramer, B.A. (1), Irvine, Robert H. Gerner, M.D., Long Beach, Barton J. Blinder, M.D., Newport Beach, CA

Summary:

Bulimia may be a distinct subgroup within the eating disorders or represent a phenomenologically distinct group with a pathophysiology similar to other eating disorders. However, the possibility of subgroups within bulimia has not been investigated. Our previous work has shown similarities between bulimics and primary anorexia nervosa (PAN) on neuroendocrine tests and others have documented that many bulimics previously met PAN diagnostic criteria. Because some bulimics exclusively utilize a single method of weight control, we investigated whether the method of weight control may be associated with biological differences within bulimia.

Subjects were 36 females diagnosed bulimic (DSM III) attending an outpatient eating disorder clinic. Age range 15 to 40; weight 80 to 119% ideal body weight (IBW). Weight control in these bulimics was achieved by either laxatives (n=5) or self-induced emesis (n=31). Patients who used both laxatives and emesis were excluded from investigation. Blood levels for LH, FSH, GH, and PRL (assayed by RIA) were obtained while patients were in a steady weight state assessed by weekly weights. Subsequently, 1 mg dexamethasone was administered at 11 pm and cortisol level was obtained at 4 p.m. (measured by RIA). Zung Depression Scale, MMPI, current and past menstrual history, and lowest adult body weight were also obtained. No patients were having normal menses. LH ($\bar{x}$=5.37$\pm$.94mIU;$p<.10$) and FSH ($\bar{x}$=3.50$\pm$.46mIU;$p<.001$) were lower and GH levels were higher (x=12.86 2.45ng/ml;p .06) in emesis subjects compared to laxative users. Taking both groups together % IBW was significantly negatively correlated with MMPI-MF Scale ($r=-.43;p<.01$) and DST cortisol ($r=-.47;p<.05$). No differences between bulimic groups were observed for psychological scales, PRL, DST response, menstrual history, or present or past % IBW. DST was abnormal ($\geq$4ug/dl) in 72% of subjects; LH and FSH were significantly lower than normal values (>2 S.D.) in 48% and 69%, respectively, of emesis subjects. These results support a biological distinction and psychological similarity of these two groups of bulimia. The relationship of these differences LH-FSH, and growth hormone to specific clinical symptoms and possible alteration in estrogen-progesterone and dopamine in emesis subjects will be discussed.

This study also confirms and extends previous reports that DST cortisol response is abnormal in eating disorders and may in part be related to weight.

These preliminary data suggest a validity for discriminating between clinical subtypes of bulimia in future studies of psychopathophysiology and treatment response.

Oral/Slide Papers

NR121 Thursday, May 10, 8:00 A.M.

IS INSULIN COMA LESS EFFECTIVE THAN HALOPERIDOL?

Steven G. Potkin, M.D. (I), Department of Psychiatry, California College of Medicine, University of California Irvine, Irvine, CA 92717; Yu-cun Shen, M.D. (I), Beijing, Peoples Rebublic of China; Herbert Pardes, M.D., New York, NY; Liang Shu, M.D. (I), Dong-Feng Zhou, M.D. (I), Beijing, Peoples Republic of China; Bruce Phelps, Ph.D. (I), Chicago, IL; R. Poland, Ph.D. (I), Torrance CA; Esa Korpi,M.D. (I), Tampere, Finland

In the 1930's and 40's, insulin coma (IC) was considered to be an effective treatment for schizophrenia. A clinical trial of IC therapy using modern evaluative techniques has been recently advocated to re-assess these claims. In China, where IC therapy is widely used, 53 drug-free DSM-III diagnosed schizophrenic patients were randomly assigned to one of the following four groups: oral haloperidol concentrate of 0.4 mg/kg; 0.15 mg/kg; 0.4 mg/kg and IC; or placebo haloperidol and IC. Clinical assessments by "blind" raters using the clinical global scale and BPRS were made at days 7, 14, 28 and 42. The haloperidol dosage remained constant throughout the study. End-point analysis using global assessment or BPRS scores demonstrated that the insulin-only group had a significantly poorer therapeutic out-come than the other three groups. BPRS analysis demonstrated that the global improvement occurred in items characteristic of schizophrenia such as uncooperativeness, unusual thoughts, and hallucinations (repeated measure covarience analyses, p 0.05). < IC combined with haloperidol offered no increased therapeutic benefit over haloperidol alone (Tukey, nonsignificant). No significant clinical difference was noted between patient groups on the two dosages of haloperidol. Analysis of the steady-state plasma haloperidol concentrations in the above groups indicated the presence of a therapeutic window between 4 and 22 ng/ml. (Unfortunately by chance the data points between 1 and 4 ng and between 22 and 26 ng are not sufficient to permit pertise characterization of the lower and upper boundaries of this therapeutic window). The 24 patients with steady state plasma levels within the 4 to 22 ng/ml therapeutic window had an average improvement of 51% compared to 20% for the 29 patients with plasma levels outside this range ($t=4.2$, $p<0.001$).

Additionally, 18 of the Chinese schizophrenics receiving 0.4 mg/kg haloperidol were sex and body-weight matched to non-Asian American schizophrenics. The American patients were also treated with 0.4 mg/kg in an identical manner. The plasma haloperidol concentration in Chinese schizophrenic patients was 52% higher than their matched American counterparts ($t=2.45$, $p<0.024$ paired t-test). These data may explain why Asians are reported to need less neuroleptic drugs and to more sensitive to side effects than non-Asians.

NR122 Thursday, May 10, 8:15 A.M.

A BLIND DSM-III FAMILY STUDY OF SCHIZOPHRENIA

Kenneth S. Kendler, M.D. (I), Medical College of Virginia, Department of Psychiatry, Box 710, Richmond, VA 23298; Alan M. Gruenberg, M.D., New Haven, CT; Ming T. Tsuang, M.D., Providence, RI

Summary:

This report examines the morbid risk for psychiatric illness in the first-degree relatives of 332 schizophrenic and 310 screened surgical control probands from the Iowa 500 and non-500 studies.

METHODS All diagnoses were made blindly by two of the authors (KSK & AMG), using DSM-III criteria. Diagnoses of the probands were made using index admission (Iowa 500) and index admission and follow-up data (Iowa non-500). Relatives were diagnosed from structured psychiatric interviews and/or hospital records, which were available for 723 relatives of schizophrenic patients and 1,056 relatives of controls. Information on 35 relatives were reviewed by both raters. DSM-III diagnoses agreed in 31 (91% agreement, kappa=0.88). Morbid risk (MR) was calculated using the Stromgren method for schizophrenia, unipolar and bipolar affective illness and paranoid disorder and the abridged Weinberg method for all other disorders. Statistical comparisons were by the difference in proportions.

RESULTS The MR for schizophrenia was significantly greater in the relatives of schizophrenic (3.7%) vs. control probands (0.2%) ($p=8.3\times10^{-7}$). In addition, the MR for schizoaffective disorder, paranoid disorder and atypical psychosis was also significantly greater in relatives of schizophrenics than in relatives of controls. No significant difference was found in the MR for unipolar or bipolar affective illness or anxiety disorder in the two groups of relatives. The MR for alcoholism was significantly less in the relatives of schizophrenics versus the relatives of controls.

COMMENT This study, which utilizes operationalized diagnostic criteria, blind diagnosis of patients and relatives, reliance on direct information on relatives (rather than indirect family history information), inclusion of a control group and a large sample size of patients and relatives, supports the hypothesis that schizophrenia as defined by DSM-III is a familial disorder. In addition, this study suggests that subgroups of patients which schizoaffective disorder, paranoid disorder and atypical psychosis have conditions which, from a familial perspective, are related to schizophrenia. As defined by DSM-III, neither affective illness, anxiety disorder nor alcoholism have a substantial familial relationship to schizophrenia.

NR123 Thursday, May 10, 8:30 A.M.

GENETIC MODELS OF SCHIZOPHRENIA

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Summary:

Seventy-nine nuclear families ascertained through chronic schizophrenic probands were examined for consistency with various genetic models. Diagnostic categories for family members included chronic schizophrenia and schizotypal personality disorder(definite and probable). Segregation analyses was employed, allowing both for arbitrary transmission probabilities, and for a mixed model, with both major locus and polygenic effects. In addition, consistency of the various models with supplementary observations(disease incidences, mating type distribution, MZ twin concordance) was examined. Our results suggested that the family data were consistent with genetic transmission, and that schizotypal personality disorder belonged in the genetic spectrum of schizophrenia. All genetic models allowing only for a single locus could not account for the family data. A simple polygenic model was not rejected in segregation analysis, and gave good agreement with supplementary observations. However, the most likely model was a mixed-recessive polygenic model, with the recessive allele having high gene frequency (0.61) and low penetrance (.017). The partition of liability variance was: major locus, 62.9%; polygenic, 19.5%; common sib environment, 6.6%; random environment, 11.0%.

NR124 Thursday, May 10, 8:45 A.M.

ATTEMPTED SUICIDE IN CHRONIC SCHIZOPHRENIA

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Summary:

Little is known about attempted suicide in chronic schizophrenia. In a consecutive series of 127 patients meeting DSM III criteria for chronic schizophrenia, 70 (55.1%) had attempted suicide. Thirty-two of these 70 patients (45.7%) had at some time had a major depressive episode meeting DSM III criteria compared with 6 of the 57 patients (10.5%) who did not attempt suicide--$p < 0.0001$. Forty-six of the 70 suicide attempters (65.7%) had received antidepressant medication at some time compared with 24 of the 57 nonattempting patients, $p < 0.01$. Eighteen of the 70 suicide attempters (25.7%) had received a course of electroconvulsive treatment (ECT) at some time compared with 4 of the 57 nonattempting patients (7.0%)--$p < 0.009$. The mean age was 25.7 years and the mean duration of chronic schizophrenic illness was 6.0 years for the 70 patients in the attempting group compared with 5.4 years for the 57 patients in the nonattempting group (no significant difference). However, the group who attempted suicide had had a mean of 5.4 psychiatric admissions (SD 3.7) compared with the mean of 3.6 psychiatric admissions (SD 2.9) of the group who did not attempt suicide--$p < 0.004$, which may be an indication that the group who attempt suicide contains patients who have a more severe relapsing chronic schizophrenic illness. The destructive effect that 5.4 psychiatric admissions in the six years from 19 to 25 years of age might have on a young adult's employment, career and heterosexual adjustment goals can readily be comprehended. CSF monoamine metabolite levels of 27 of these patients who at some time had attempted suicide were compared with those of 27 of these chronic schizophrenic patients who had never attempted suicide. There were no significant differences between either the violent or nonviolent attempters and those who had never attempted suicide on the mean lumbar CSF concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA), the dopamine metabolite homovanillic acid (HVA) or the norepinephrine metabolite 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG).

NR125 Thursday, May 10, 9:00 A.M.

BRAIN IMAGING AND NEUROLEPTICS IN SCHIZOPHRENIA

Richard J. Haier, Ph.D. (I), University of California, Department of Psychiatry, Irvine, CA 92717; William Braden, M.D., Providence, RI

Summary:

We are studying changes in the brain cortex electrical activity in Schizophrenia. The aims are to determine: 1) if the onset of neuroleptic treatment alters electrical activity in some cortex locations more than others; 2) if changes in cortex electrical activity over time are related to the course of neuroleptic treatment, and 3) if changes in cortex electrical activity are related to the course of the illness.

Each patient undergoes a series of visual evoked potential testing sessions. The first session occurs shortly after hospitalization while the patient is off medication. The next session occurs just before the first dose of neuroleptic medication is administered. Additional sessions are completed 1, 2, 6, and 24 hours after the initial dose. Subsequently, the patient is tested, on average, every 3 or 4 days for a 2-4 week hospitalization. Evoked potential testing session is the same and results in a 15-site topographic computer map showing the distribution of evoked potential parameters over the left lateral cortex.

Results indicate that 1) neuroleptics acutely reduce evoked potential amplitudes all over the cortex; 2) systematic changes in the frontal lobes are related to drug treatment; and 3) increases in frontal lobe amplitudes over time correspond to clinical improvement (see Figure 1).

Because the evoked potential mapping procedure is completely nonintrusive and without risk, its repetitious use to study changes over time is an important advantage over other imaging techniques. Additional applications of this method and strategy will be discussed.

NR126 Thursday, May 10, 9:15 A.M.

OUTCOME PREDICTION IN CHRONIC SCHIZOPHRENIA

Thomas H. McGlashan, M.D., Chestnut Lodge Research Institute, 500 West Montgomery Avenue, Rockville, MD 20850

Summary:

Are there robust predictors of long-term outcome in schizophrenia beyond the initial episode(s)? This seldom studied question is addressed by testing for predictors among a sample (N=163) of largely chronic DSMIII schizophrenic patients (80% ill for more than 2 years) from The Chestnut Lodge Follow-Up Study.

Multidimensional outcome was assessed by interview 15 years (average) post-discharge (range 2-32 years). Each patient's medical record was independently abstracted (ie, blind to follow-up) for rediagnosis by current criteria and for ratings of multiple predictor variables (N=153) from four broad categories suggested by the literature: general background (eg, demography), premorbid characteristics, psychopathology and course of illness (chronicity). Only variables with acceptable interrater reliabilities were studied. Six outcome dimensions were selected: further hospitalization, employment, social activity, intimacy, symptomatology, and global functioning. Highly significant correlations ($p<.001$) between individual predictors and each outcome dimension were identified. Significant sets of predictors were also identified for each outcome dimension using multiple regression and discriminant function analysis.

Predictors accounted for approximately 1/3 of the outcome variance across all outcome dimensions, thus demonstrating substantial predictor effects for this chronic schizophrenic population. The following variables regularly (ie, individually and as components in multivariate equations) predicted better global outcome: less family history of schizophrenia, better premorbid instrumental functioning (interests and skills), more affective signs and symptoms (especially depression) in the manifest psychopathology, and absence of psychotic assaultiveness. Important predictors of the other outcome dimensions will also be presented. As with more acute populations, premorbid characteristics were important and relatively specific, ie, outcome dimensions tended to be predicted most effectively by their corresponding premorbid variables. In contrast to more acute populations, chronicity (course of disorder) receeded whereas manifestations of psychopathology (genetics, signs and symptoms) emerged in predictive power. Overall, results demonstrate the existence of "late prognostic" predictors of outcome in schizophrenia other than chronicity measures. Furthermore, these seem to identify "virulence" of the disorder and initial (baseline) strength of the afflicted personality as key.

NR127 Thursday, May 10, 9:30 A.M.

CT CORRELATES OF COGNITIVE DEFICITS IN SCHIZOPHRENIA

Anand Pandurangi, M.D., Columbia University, Department of Psychiatry, 722 W. 168th Street, New York, NY 10032, Robert Bilder, A.B. (1), Ronald Rieder, M.D., Sukdeb Mukherjee, M.D., Janos Kurucz, M.D., New York, NY

Summary:

The traditional notion that basic intellectual functions are intact in Schizophrenia is being gradually replaced by an awareness,brought about by an intensive use of batteries of neuropsychological tests, that certain discrete deficits exist either at the onset or develop during the course of this illness. CT scanning of the brain has made it possible to study the structural correlates of such deficits. We present data that elucidate the nature of cognitive deterioration in Chronic Schizophrenia and associate different types of clinical deficits with different CT measures.

35 patients diagnosed as having Chronic Schizophrenia(using RDC and DSM-III) underwent Psychiatric and neuropsychological assessment on a research unit. Psychiatric rating scales included the SADS-PD, BPRS, Negative Symptom scale and Pre-morbid adjustment scale. The neuropsychological task battery consissted of an assortment of tests aimed at studying regional and diffuse brain damage. From these tasks 'deterioration quotients' were constructe d based on the difference in the performance of those tasks thought to be vulnerable to organic damage and those that aren't. During the same period patients underwent a CT scan that yielded 10-12 slices per subject. From computerised tracings indices of ventricle size such as Frontal Horn Index(FHI) and Ventricle-Brain Ratio(VBR) were derived. Ratings of sulcal prominence(SPR) were obtained by blind raters on a standardised 6 point scale based on visual reading of cortical sulci and interhemispheric and sylvian fissures.

We found that those Schizophrenics having greater deterioration quotients had more prominent sulci(r range 0.6-0.7, $p<0.05$) and larger FHI(r range 0.6-0.72,$p<0.05$). VBR, on the other hand was not significantly associated with deterioration indices but was significantly related to poor premorbid adjustment($r=0.50, p<0.05$).
Our data supports previous reports of cognitive deficits in Chronic Schizophrenia and indicat es that this may have demonstrable structural basis. Further prominent sulci and increased VBR may be associated with different types of Clinical deficits.

NR128 Thursday, May 10, 9:45 A.M.

NEUROPSYCHOLOGICAL PROFILES OF +/-SCHIZOPHRENIA

Ronald O. Rieder, M.D., New York State Psychiatric Institute, 722 West 168th Street, New York, NY 10032, Anand Pandurangi, M.D., Robert Bilder, Ph.D. (I), Shukdeb Murkerjee, M.D., Janos Kurucz, M.D., New York, NY

Summary:

The clinical evaluation and subtyping of schizophrenia has been attempted both by psychiatrists, using psychiatric symptomatology, and by neuropsychologists, using test performance measures. Various psychiatric classifications have been proposed, but recent proposals have focused on a positive/negative symptom dichotomy. Neuropsychological assessment of schizophrenia has usually evaluated the presence or absence of global impairment with the Halstead-Reitan or similar batteries, but other techniques allow for better localization of brain dysfunction and specification of functional disturbances. Comparisons between the methods of the two disciplines are few, and comparisons of the +/- dichotomy with the newer neuropsychological methods are practically non-existent.

In an interdisciplinary study of 35 chronic schizophrenic inpatients (mean age = 30 + 11), detailed clinical evaluations (SADS, SANS, BPRS etc.) and comprehensive neuropsychological evaluations (50 tests selected to yield indices of regional, functional and global impairment) were compared. A strong relationship was found between negative symptoms and several measures of global/diffuse impairment (r's = .50-.55). Positive symptoms, on the other hand, were strongly related to measures of regional (left hemisphere and anterior) dysfunction (r's = .55-.60), and specific functional (motor and language) impairment (r's = .55-.60).

An apparent conflict has existed between some investigations finding relatively localized neuropsychological or neurometabolic abnormalities in schizophrenia (Flor-Henry, Ingvar, Golden, Buchsbaum) and other studies using similar techniques which have indicated that the brain disturbance is diffuse (eg. Matthews). Our results suggest that this discrepancy might be explained by symptom characteristics of the samples. It is likely that diffuse abnormalities of function and metabolism are observed primarily in "negative symptom schizophrenia," while "positive symptom schizophrenia" will manifest the localized (left and anterior) dysfunction which the investigators listed above have found. We belive that these data validate the new methods of clinical evaluation developed separately by each discipline and that together these methods can help in establishing subgroupings of schizophrenic patients that will aid in the analysis of EEG, CT,PET, rCBF and biochemical data.

NR129 Thursday, May 10, 10:00 A.M.

FRONTAL CORTICAL DYSFUNCTION IN SCHIZOPHRENIA

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Summary:

Many of the clinical symptoms, neurological signs, cognitive deficts, and neurophysiological findings associated with schizophrenia suggest dorsolateral frontal lobe dysfunction. The application of innovations in functional "brain imaging" have also implicated the frontal cortex, but studies have been difficult to interpret because patients have been evaluated either at rest or while on medication.

Thirty patients with chronic schizophrenia ($\bar{x}$ age 28 $\pm$ 6, 15 patients medication-free for at least four weeks and 15 receiving neuroleptics) and 20 healthy volunteers ($\bar{x}$ age 31 $\pm$ 8) completed a series of three consecutive Xe^{133} inhalation rCBF procedures designed to evaluate dorsolateral frontal cortical function: the first procedure at rest, then while performing a simple number matching task (NM) and while taking an automated version of the Wisconsin Card Sort Test (WCS). The latter two conditions were performed in counterbalanced sequence. A second study was designed to test the possibility that changes in rCBF might not be specific to the WCS frontal cortical task, but might relate instead to any demanding cognitive test. In this protocol, 10 patients medication-free for at least four weeks and 10 healthy volunteers underwent a counter-balanced three trial Xe^{133} inhalation study doing a visual continuous performance task (CPT) with and without dynamic pacing.

A relative increase in frontal flow (Frontal Index (FI) > 1) was seen in all groups at rest and its magnitude (FI) did not differ. In the medication-free WCS study, the patients showed a slight decrease in FI during NM ($p < .02$) and a marked reduction during WCS ($p < .001$), with seven patients becoming hypofrontal (FI < 1) as compared with none of the controls ($p < .01$). A probe by probe across group analysis showed significantly reduced CBF for the schizophrenics in one of 12 frontal probes at rest, none during NM, and eight during WCS. In the medication WCS study, the same pattern of findings emerged. Ten of the patients became hypofrontal during WCS. A probe by probe analysis of the CPT data revealed no significant differences between patients and controls on either X or A-X conditions despite poorer patient performance.

These results are consistent with disordered dorsolateral frontal cortical activation in schizophrenia. The finding appears to be independent of medication state and to be limited to dorsolateral frontal cognitive demand. A disorder of afferentation is implicated.

NR130 Thursday, May 10, 10:15 A.M.

PLASMA HOMOVANILLIC ACID CORRELATES WITH NEUROLEPTIC EFFECTS

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Summary:

Reduction in functional CNS dopamine (DA) activity produced by the post-synaptic blockade of DA receptors has been the hypothesized mechanism by which neuroleptic drugs produce antipsychotic effects. The discrepancy between the time course of DA blockade by neuroleptic drugs (rapid) and therapeutic efficacy (time-delayed), however, has been a persistently weak link in the DA hypothesis of neuroleptic action. Since there is now considerable evidence suggesting that fluctuations in plasma levels of the major DA metabolite, homovanillic acid (HVA), parallel changes in DA release or "turnover" in the CNS, we have carried out a study in which we have longitudinally measured plasma HVA in patients with DSM III diagnosed schizophrenia (N=8) both before (mean ±SEM medication-free days: 28 ±6) and during treatment with the neuroleptic, fluphenazine (mean ±SEM daily dose: 36 ±6 mg/day). Fluphenazine administration resulted in a significant ($p<.001$) time-delayed decrease in plasma HVA from pretreatment levels which were also significantly elevated when compared to those of age- and sex-matched healthy controls ($p<.05$). Following 3, 4 and 5 weeks of fluphenazine treatment plasma HVA levels were significantly lower than those observed during the pretreatment phase of study ($p<.05$, $<.01$, $<.05$, respectively); these decreases resulted in levels of plasma HVA in schizophrenic patients comparable to controls. Both the absolute levels as well as the neuroleptic-induced reductions in plasma HVA were highly correlated with ratings of global psychosis ($r=.82$, $p<.001$) and improvement in psychosis ($r=.87$, $p<.001$), respectively. Our findings of a time-dependent decrease in plasma HVA during neuroleptic treatment in schizophrenic patients demonstrates an adaptational change in DA release or "turnover" consistent with that previously reported in animal studies, and for the first time links this pattern to the therapeutic effects of neuroleptic treatment in schizophrenic patients. These data, therefore, support the hypothesis that the mechanism of action of neuroleptics, like fluphenazine, involves a decrease in dopamine "turnover" and that monitoring changes in plasma HVA may be a useful tool in assessing the antipsychotic activity of pharmacologic agents.

NR131 Thursday, May 10, 10:30 A.M.

CEREBROSPINAL FLUID, HOMOVANILLIC ACID IN TARDIVE DYSKINESIA

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Summary:

Tardive dyskinesia (TD) is a disorder characterized by involuntary repetitive movements which develops during chronic neuroleptic therapy. A possible pathophysiologic mechanism responsible for this disorder is dopamine (DA) receptor supersensitivity in the nigrostriatum. Determination of homovanillic acid (HVA), a DA metabolite, in the cerebrospinal fluid (CSF) provides an indirect measurement of central dopaminergic activity, a large percentage of which originates in the nigrostriatum. If patients with TD have both a pre and post-synaptic DA receptor supersensitivity, they would be expected to present with higher feedback inhibition of DA secretion, decreased DA turnover and diminished HVA production. Apomorphine (APO), a DA agonist, acts preferentially at presynaptic receptors when given in low doses and therefore decreases HVA production. When administered to patients with TD, a greater diminution of DA turnover and HVA production would be predicted by the supersensitivity hypothesis. Methods - Subjects were 22 schizophrenic male inpatients, 8 of whom had TD. The mean age for the TD group was 43 $\pm$ 13, and 35 $\pm$ 9 for the non-TD group. Diagnosis of schizophrenia was made by RDC and Feighner criteria. All patients were in an exacerbated psychotic state of their chronic illness. Patients were assessed for TD by two raters using the AIMS scale. TD was strictly defined as the presence of moderately severe facial movements (a rating of 3 on any of the first 4 items on the AIMS) with or without concurrent limb and trunk movements. All patients were drug-free for at least 2 weeks and had not received depot neuroleptics for at least 1 month prior to study. Patients were on a low monoamine diet for a minimum of 3 days prior to studies. Apomorphine 0.75 and an equal volume of saline placebo was administered subcutaneously on random non-sequential days at 10:30 am. Subjects had been pretreated with probenecid (100 mg/kg) in divided doses beginning the evening prior to each study day. Lumbar punctures were performed at 1400 after the patients had been recumbent for approximately 15 hours. Standard aliquots of CSF were assayed for HVA and probenecid concentration by HPLC. Results - Since there is a correlation between CSF probenecid concentration and monoamine metabolites, ratio of HVA to probenecid better reflects the accumulation of this metabolite than HVA concentration alone. Age correlates with CSF, HVA therefore analysis of covariance using age as a covariant was performed. Mean CSF, HVA ratio to CSF probenecid after APO administration in the TD group was 8.69, significantly lower than the non-TD group 12.06, $p < .01$. This difference between the two groups persists even when CSF probenecid concentration is not accounted for. Mean CSF, HVA concentration for the TD group was 148.28 ng/ml and for the non-TD group 256.88 ng/ml, $p < .04$. In conclusion, the data shows a lower CSF, HVA concentration in the TD schizophrenics consistent with a state of DA receptor supersensitivity in those patients. Additional clinical correlates and endocrine profile of the TD and non-TD patients will be discussed.

NR132 Thursday, May 10, 10:45 A.M.

DOPAMINE AND NONDOPAMINE PSYCHOSES

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Summary:

Though the neuroleptic drugs have been described as producing therapeutic effects by means of reduction of putative dopamine-related hyperactivity, the time course of antipsychotic effects following introduction of neuroleptic drug is not consistent with such mechanisms. Within hours after the initiation of average doses of neuroleptic, post-synaptic dopamine receptor blockade (D_2 and D_1) is virtually complete. Yet only a small subsample of the psychotic population (rapid responders [RR]) improves dramatically during this early period and goes on to substantial (60%) recovery within the first week of continued neuroleptic drug administration. The majority of psychotics (classical responders [CR]) require two to six weeks of daily drug administration for similar reduction of psychotic symptoms. For such CR, blockade of post-synaptic dopamine receptors and cessation of dopamine mediated neurotransmission is not associated with immediate symptom reduction.

We have explored the sensitivity of post-synaptic dopamine receptors in drug free psychotics found to be RR or CR following average doses of neuroleptic. The post-synaptic effects of a dopamine receptor agonist was monitored by the peak release of GH into the plasma 60+20 minutes following injection of 0.75 mg apomorphine.

RR had a mean ($\pm$SD) GH peak response of 24.0 ± 5.3(n=6) while CR had a peak GH response of 10.3 ± 2.0(n=15). The GH peak response was significantly exaggerated ($p<0.01$) in the RR as opposed to the CR.

Exaggerated sensitivity of post-synaptic DA receptors and rapid antipsychotic response following DA receptor blockade in RR suggest a true functional DA hyperactivity disorder in the RR group. In contrast, lower post-synaptic receptor sensitivity (as reflected by a lower GH response to apomorphine) and failure of early response to DA receptor blockade in CR focuses attention away from DA hyperactivity as a relevant etiologic mechanism in CR's.

Response rates to neuroleptic drugs and neuroendocrine probes of receptor sensitivity may separate two or more etiologically distinct diseases which present with schizophrenic-like psychoses.

NR133 Thursday, May 10, 11:00 A.M.

LITHIUM ANTAGONIZES ALCOHOL INTOXICATION

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Summary:

For a decade there have been reports that lithium maintenance is beneficial in the treatment of alcoholics, but neither the clinical efficacy nor the behavioral mechanisms by which therapeutic benefits from lithium might accrue to alcoholics have been fully established. In this study, alcoholics were pre-treated with lithium and then challenged with a standardized dose of ethanol. METHODS: 35 medically healthy detoxified male alcoholics participated in a repeated measures, split-half crossover design. Lithium carbonate and placebo were administered under double-blind. After 14 days on lithium (mean serum level=0.89 mEq/L) and placebo, subjects participated in two identical experimental sessions which consisted of self-rating scales and a Cognitive Test Battery before and after the administration of 1.32 mL/kg of 95% ethanol. (Mean blood alcohol level was .104 g/dL.) RESULTS: Alcoholics on lithium reported less intoxication (p=.01) and decreased urge to continue drinking (p=.003). They also felt less confused and bewildered from ethanol while on lithium (T=3.71; p=.01). Ethanol alone (i.e., Placebo Condition) produced marked performance decrements on the Cognitive Battery. Lithium's effect on the ethanol-induced decrement varied. It had no effect on the Porteus Maze and reduced rate of performance on the Standardized Serial Seven. It slowed performance, but decreased errors on the Speed of Closure. Lithium almost completely reversed ethanol's effect on the Minnesota Clerical (more items completed, correct, and fewer errors) and on the Trail Making A Test. DISCUSSION: Alcoholics on lithium reported less intoxication, a decrease in the desire to continue drinking and less cognitive dysfunction when challenged by standardized doses of ethanol. Lithium significantly attenuated the ethanol-induced decrement in cognitive performance. No differential lithium effect was noted when alcoholics were divided by diagnoses of affective disorder vs. no affective disorder. Previously, it has been hypothesized that lithium's therapeutic benefit in the alcoholic is due to the mood stabilizing properties lithium exerts in depressed alcoholics. Our data suggest that in addition to mood normalization, that lithium's capacity to directly effect ethanol intoxication may also help explain its potential therapeutic efficacy in alcoholism. Lithium's antagonism of ethanol-induced disruption of cognition may allow the alcoholic to exert greater control over drinking behavior during intoxication. This is further confirmatory evidence that lithium may be useful in the treatment of alcoholics.

NR134 Thursday, May 10, 11:15 A.M.

ENDORPHINS AND OPIOID DEPENDENCE

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Summary:

CSF samples were obtained from human opioid addicts (mean duration of dependence: 12 years) in four defined clinical states: dependent, withdrawal, naltrexone and drug-free. Endorphin activity was determined by radio-receptor assay in all samples (N=86) and by radio-immuno assay (RIA) for specific peptides in selected samples. Addicts in all four clinical states generally showed high endorphin levels as compared to non-addict controls. Fraction I endorphins were significantly correlated with years of addiction and time since last dose of opioid. Endorphin levels fell during acute withdrawal and rose again during drug-free and naltrexone states. Fraction I showed a "U" shaped function over the first 72 hours of withdrawal with an apparent rebound during late withdrawal. Diazepam was given to a small number of subjects in withdrawal to relieve anxiety during the lumbar puncture. The diazepam tended to increase endorphin levels during acute withdrawal.

Peptides for which antibodies were available (met-enkephalin, β endorphin, substance P and dynorphin 1-17) were found in very low levels in those samples. Thus the identity of the substances producing the increased endorphin activity is so far unknown.

CSF was also obtained in two closely-related species of macacaque monkeys in clinical states similar to human addicts. While the rhesus species readily developed tolerance to opioids, the cynomolgus failed to show tolerance and, in fact, became sensitized to opioids (Ternes et al., 1983). Fraction I endorphins in the CSF of the cynomolgus was significantly ($p<.01$) higher than that of the rhesus while Fraction II endorphins showed no quantitative differences between the two species.

These findings suggest a complex dynamic relationship between opioid dependence and endorphin systems including probable receptor changes in the tolerant state. Recent evidence (Nyberg et al, 1983) indicates that Fraction I is largely composed of dynorphin related peptides and this is the fraction most sensitive to the addictive states studied here.

NR135 Thursday, May 10, 11:30 A.M.

SOCIAL DRINKING, PLATELET MONOAMINE OXIDASE, AND CT SCAN VENTRICULAR BRAIN RATIO

T. Peter Bridge, M.D., ADAMHA, Room 13C-23, Parklawn Building, 5600 Fishers Lane, Rockville, MD 20857, E.S. Parker (I), C.E. Bickham (I), Bethesda, MD; L. Ingraham (I), Washington, DC; J. Blouin (I), Ottawa, Ont., Canada

Summary:

Documented previously is the observation of alcohol abuse/dependence associated with enlarged cerebral ventricular/brain ratio (VBR). Activity decrements of platelet monoamine oxidase (MAO) have also been observed to be associated with alcoholism and to be a potential genetic marker for the development of alcoholism. Although alterations of the VBR are associated with changes in cognitive function in alcoholics, it remains unclear whether alcohol exerts a direct toxic effect resultant in VBR increments in only alcoholics. Reported here for the first time is a study of 47 adult social drinkers receiving brain CT scans for non-tissue destructive/space occupying reasons, where a multivariate model containing age, height, and educational status variables and a thermolability measure for platelet MAO activity, a weighted average alcohol consumption measure (amount x frequency), an interaction term for alcohol consumption and age, and a quadratic term for age explains approximately 60% of the variance in CT VBR scores in this sample. Each term contributes significantly to the explanatory power of the complete model. Using a forced entry, stepwise multiple regression, the prior entry of demographic and MAO variables control for their effects on VBR prior to examining the relationship of the alcohol variables on VBR. Given the significant increment in explanatory power associated with the alcohol variables, the data from this sample support the hypothesis that alcohol has direct toxic effects on neuroanatomic measures. Furthermore, these effects are separate from and in addition to those accounted for by demographic and MAO variables. The presence of alcohol interaction term and a quadratic term for age indicate that moderate to heavy social drinking demonstrates differential effects on VBR from other social drinking patterns. The effect of moderate to heavy social drinking in this sample is to demonstrate marked increments in VBR past the age of 40. The data analysis from this sample argue for the conclusion that social drinking patterns impact upon VBR measures separately and additively to "predisposition" or biologic marker variables. These data have serious implications for the prevention of future medical service demands by the aged, the U.S. population segment that is increasing relatively and absolutely.

NR136 Thursday, MAY 10, 12 Noon-2:00 P.M.

DURATION CRITERIA AND OUTCOME IN MAJOR PSYCHOSES

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Summary:

Washington Univ. (Feighner) criteria require a six-month duration of symptoms for schizophrenia, but only of two weeks for mania and one month for depression. Could this six-month criterion for schizophrenia explain its significantly worse outcome compared to affective disorder? Does six-month criterion for schizophrenia according to Feighner and DSM-III select a chronic group of patients who would do poorly regardless of diagnosis?

To examine this question, we analyzed our 40-year-outcome data of 186 schizophrenics (S), 86 manics (M), and 212 depressives (D) diagnosed according to Feighner criteria. Of these, 21 manics (24%) and 121 depressives (57%) had duration of symptoms of six months or more ($\geq$ 6 mo.) before index admission. They were compared to the 186 schizophrenics, to each other and to their counterparts, 65 manics (75%) and 91 depressives (43%) with fewer than six months of symptoms ($<$ 6 mo.) in terms of their psychiatric and occupational outcome at the time of our personal follow-up.

Table 1 shows that regardless of duration, the affective disorders had a significantly better outcome than schizophrenia ($p < .001$). Six-month duration manic and depressives fared just as well as their shorter duration counterparts (no significant differences). Thus, the six-month duration criterion alone does not account for the difference in outcome between schizophrenia and affective disorder. Future studies should concentrate on the identification of other specific variables which are important in separating long-term outcome of schizophrenia and affective disorders.

Table 1

Diagnostic Groups		S	M $\geq$ 6 mo.	D $\geq$ 6 mo.	M < 6 mo.	D < 6 mo.
Number of Patients		186	21	121	65	91
Good Outcome*						
Psychiatric	n(%)	38(20)	11(52)	71(59)	32(49)	58(64)
Occupational	n(%)	65(35)	17(81)	78(64)	41(63)	64(70)

*Psychiatric: Free of symptoms; Occupational: Gainfully employed, or retired

NR137 Thursday, May 10, 12 Noon-2:00 P.M.

HALOPERIDOL CONCENTRATION AND CLINICAL RESPONSE

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Summary:

A number of authors have proposed that a "therapeutic window" may exist for haloperidol treatment of schizophrenia, with optimum response occurring when serum concentration is in the range of approximately 5 to 15 ng/ml.

METHODS: To test this hypothesis 23 chronic schizophrenic inpatients were withdrawn from their admission neuroleptic medication and placed on coded placebo for six weeks. They were then given a fixed dose of coded haloperidol (0.4 mg/kg) for six weeks. Patients were rated twice daily by ward nursing staff "blind" to medication status using a scaled version of the BPRS. Serum haloperidol concentrations were determined at 2, 4 and 6 weeks using high pressure liquid chromatography.

RESULTS: The steady state serum concentration of haloperidol in this group of patients varied from 6.8 to 32.4 ng/ml. At 2, 4 and 6 weeks the correlations of percent improvement of total BPRS ratings versus serum haloperidol concentration were -0.24, +0.41 and +0.15 respectively (Pearson r). None of these correlations were statistically significant and there was no trend suggestive of a curvilinear pattern. In fact, comparing the patients having serum concentrations above and below 15 ng/ml revealed no difference in improvement; the 8 patients with concentrations greater than 15 ng/ml had mean BPRS improvement of 24% and those below 15 ng/ml had a mean improvement of 25%.

DISCUSSION: The results in this group of patients do not support the proposed existence of an upper therapeutic limit for serum haloperidol concentrations. It should be noted, however, that although higher concentrations were not necessarily detrimental, they did not lead to any greater improvement in this group of patients. The difference between our results and previous reports will be discussed.

NR138 Thursday, May 10, 12 Noon-2:00 P.M.

SALIVARY AND SERUM NEUROLEPTIC LEVELS IN MAN

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Summary:

Patients treated with identical doses of antipsychotic medication show great interindividual differences in their steady state plasma neuroleptic levels. To establish a relationship between the administered dose and the magnitude of drug effect, blood level determinations are of great importance. The theoretical importance of pharmacokinetic studies of antipsychotic drugs is not always reflected in common psychiatric practice, because of the cumbersome and discomforting blood sampling procedures during multiple serial sample collections from psychiatric patients. Drug concentrations in saliva are often proportional to the concentrations in plasma and may be substituted for plasma. To study the relationship of serum and salivary neuroleptic levels we conducted pharmacokinetic studies on molindone in four normal male control subjects (21-37 years) who ingested a 50mg dose of molindone, and in three schizophrenic subjects (20-50 years) receiving thioridazine. Levels were determined by radioreceptor assay using rat caudate as a source of high affinity dopamine receptors and ^{3}H-spiroperidol as the radioligand. Blood samples were collected from an i.v. catheter. The saliva was collected by placing a double walled vacuum cup (modified Teflon-Lashley cup) over the Stensen's duct opening. On analysis, both blood and salivary molindone levels in controls displayed a biphasic pharmacokinetic response curve. In the initial phase, blood and salivary levels were steadily increasing from 0 to 60 minutes, indicating the absorbtive phase which was followed by a steady decline in both salivary and blood molindone levels over the next 6 hours representing the distributive phase. There was a good positive linear relationship between serum and salivary molindone levels ($r = 0.796$). The saliva/serum ratio was greater than one in the absorbtive phase, but it was less than one in the elimination phase. In schizophrenics, salivary levels were undetectable when blood levels were less than 100ng/ml, a concentration below the therapeutic range. There was a good correlation between antipsychotic serum and salivary levels and Brief Psychiatric Rating Scale scores ($r = -0.70$ and -0.65 respectively). Our data demonstrate that measurement of neuroleptic levels in saliva represents a non-invasive technique which is highly correlated with blood levels. Furthermore, as saliva is an ultrafiltrate of plasma, salivary levels may more accurately reflect the true availability of drug able to penetrate the blood-brain barrier.

NR139 Thursday, May 10, 12 Noon-2:00 P.M.

LOW DOSE DRUG TREATMENT OF CHRONIC SCHIZOPHRENIA

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Summary:

The general effectiveness of neuroleptics in the treatment of chronic schizophrenia is well established. However, specific questions regarding the optimal neuroleptic dose range, therapeutic plasma levels and management of side effects complicates the use of these drugs. Also, response to neuroleptics among patients with chronic disease is variable and the extent to which this can be accounted for by kinetic parameters is unclear. We have undertaken a systematic study of the effectiveness of low dose haloperidol in schizophrenic inpatients and have correlated clinical improvement with drug dose, drug level in plasma and CSF, and plasma levels of prolactin (PRL) to identify factors predictive of clinical response.

In a double-blind study 11 chronic psychiatric inpatients, all of whom met DSM III criteria for schizophrenia and who had been drug-free for at least one month, were randomly administered haloperidol (0.1 and 0.3 mg/kg, p.o.) or placebo in 4-week trial periods. During the final 2 weeks of each treatment, plasma levels of haloperidol and prolactin were assessed and mental status was rated with the BPRS. CSF levels of haloperidol were measured once in each drug period.

HALOPERIDOL		BPRS		PRL
Dose	ng/ml	Total Score	Psychosis Score	ng/ml
Placebo	0	56.0	11.8	9.45
0.1 mg/kg	2.75	49.3	10.7	22.0
0.3 mg/kg	8.94	46.3	9.6	61.3

The data demonstrate both significant clinical improvement as the dose of haloperidol increased ($p < .025$) and a positive correlation between clinical response and plasma PRL and haloperidol levels. As anticipated, however, there was considerable variability in the response of individual patients to these two doses of haloperidol. Some patients showed maximum improvement at the lowest dose, some showed no improvement until they were given the higher dose, others demonstrated progressive improvement as the dose of neuroleptic increased and still others showed no improvement or worsened when administered haloperidol.

Several explanations may account for the variation in individual response of these patients. These include: (1) interpatient differences in the pharmacokinetics of drug distribution, (2) interpatient differences in the pharmacodynamic response to neuroleptics, or (3) the schizophrenic population sampled may represent heterogenous disease states involving different neuropathologic mechanisms. Attempts to account for individual variable response will be discussed.

NR140 Thursday, May 10, 12 Noon-2:00 P.M.

ACETY CHOLINE RECEPTOR AUTOANTIBODIES TO TARDIVE DYSKINESIA

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Summary:

Autoantibodies are known to produce a variety of pathologic conditions in man. Drug induced immune reactions resembling spontaneously occurring diseases have previously been reported. Various psychotropic drugs including neuroleptics have been associated with abnormal homoral and cellular immune features and can produce conditions that resemble connective tissue diseases and affect neuromuscular transmission. Tardive dyskinesia (TD) is an abnormal involuntary hyperkinetic movement disorder that can occur as a consequence of exposure to neuroleptic drugs, and is believed to reflect hyperdopaminergic and hypocholinergic neuronal activity within specific locations of the CNS. To explore the possible role of immunologic mechanisms in the pathogenesis of TD we assayed sera from 34 patients with tardive dyskinesia and 23 nonpatient normal controls for antibodies (AB) to nicotinic acetyl choline receptors (AChR). Serum I_gG against AChR was measured by immunoprecipitation assay and expressed as moles of alpha-bungarotoxin binding sites x^{10-9}. The patient group had significantly higherAB titers (x .27nm/L S.D. .31) than the control groups (x .006nm/L S.D. .01) ($p < .001$). We established a criterion value 0.05 nm/L (greater than 2 standard deviations from the mean of control values) to dichotomize AB titers into normal and abnormal. 22 of the 34 psychiatric patients had AB titers $>$ .05nm/L. 19 of these had titers $>$ .1nm/L. Patients with elevated AB titers were significantly older, had longer durations of illness and treatment, and were more likely to have a history of extrapyramidal side effects (EPS).Surprisingly, patients with elevated AB titer had had less treatment with antiparkinsonian drugs at the time of blood collection. In the 12 patients not receiving neuroleptics at the sample collection AB titers were positively correlated with length of time off neuroleptics ($r' = .61$, $p = .04$). No differences were found between those patients off neuroleptics for only a short time (less than 3 months) and patients on neuroleptics at time of the exam. The abnormal AB levels are in the range seen in patients with mild generalized myasthenia gravis. Normally this AB would not be present in measurable concentrations. In our sample, diagnosis did not have a significant effect. The fact that a significant relationship was found between treatment condition, both prior history and at the time of exam, and AB levels suggests the influence of treatment. Bradley et al, have suggested that drug induced autoimmunity may be involved in the pathogenesis of TD.

NR141 Thursday, May 10, 12 Noon-2:00 P.M.

NEUROLEPTIC BLOOD LEVELS AND TARDIVE DYSKINESIA

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Summary:

Tardive dyskinesia (TD) results from exposure to neuroleptic drugs and preliminary data suggests that higher blood levels of neuroleptics are associated more often with tardive dyskinesia. Moreover, many early cases of TD are missed due to covert dyskinesias, namely dyskinesias masked by the neuroleptic agent. We have embarked on a study to correlate the blood levels of neuroleptics as they relate to TD as rated with the Abnormal Involuntary Movement Scale (AIMS). In our preliminary investigation we studied 5 chronic male schizophrenic subjects between 34-56 years old who had a long history of neuroleptic drug intake. All patients were receiving thioridazine, in doses ranging from 400-800mg daily. Neuroleptic medication was slowly tapered over two weeks, and after a one week drug washout, the neuroleptic was reintroduced at its prestudy dosage level. On a weekly basis blood was collected for the measurement of levels and the AIMS was administered. The neuroleptic blood level was ascertained using the radio-receptor assay in which patient serum was used to displace ^{3}H-spiroperidol from binding to dopamine receptors harvested from rat caudate-putamen nucleus; all levels are expressed as ng/ml in chlorpromazine equivalents. Interindividual variations in blood levels were wide, as two individuals, both receiving 800mg thioridazine showed blood levels of 3570ng/ml and 470ng/ml respectively, however changes in individual blood levels correlated strongly with changes in dosage. In no cases was thioridazine capable of consistently suppressing totally even minimal dyskinesias. Although not producing total suppresssion of abnormal movements, the tapering and discontinuation of thioridazine did result in increased dyskinetic activity. There was a negative correlation between blood level and global abnormal movements, with dyskinesias of the tongue and jaw correlating best (as high as $r = -0.95$) with neuroleptic level. The data also show that levels above 300ng/ml produced significant masking of movements. These data show that blood levels of thioridazine do correlate with central dopamine receptor blocking activity in man, and therefore validating the utility of these measurements. We have also demonstrated that patients with blood levels greater than 300ng/ml are likely to have a masking of dyskinetic movements.

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RESERPINE AND NEUROLEPTICS FOR REFRACTORY PSYCHOSES

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Summary:

Reserpine was combined with conventional doses of neuroleptics in the treatment of 36 adult patients in longterm psychiatric hospital treatment who had previously demonstrated minimal or negligible response to neuroleptics or lithium therapy of manic, schizoaffective, or schizophrenic psychoses. Duration of illness had varied from 5 to over 25 years, with predominantly poor functioning for those who had spent time out of institutions. Most patients studied had spent extensive periods of time living in highly structured institutional settings and were not regarded as treatment responders.

Reserpine was increased in most cases in weekly increments of 0.25 mg bid until psychotic symptoms were minimized or symptoms of intolerance developed to a point where clinical judgment dictated discontinuation of the trial. Most patients were treated in the 1.5 to 4.0 mg daily range.

Overall, 50% of treated patients demonstrated a partial to dramatic treatment response, in which symptoms of agitation, hallucinations, delusions, emotional lability, and poor impulse control were substantially reduced. These changes were in marked contrast to the longterm course of these patients or previous lack of response to other psychoactive agents. Within the total group, 25% demonstrated a good response, and 16% demonstrated a dramatic reduction in psychotic symptoms. A number of responders were able to be discharged from the hospital at a much earlier time than clinically expected. Most notably, 8% underwent total remission of psychosis, permitting successful return to the community from the hospital and hospital-free time without recurrence of psychotic symptoms for at least a year.

Reserpine appears to have antipsychotic effects independent of those of neuroleptics. Four theoretical explanations for this difference are reviewed.

Reserpine in combination with neuroleptics appears to be clinically helpful in the treatment of refractory psychoses and may well be underutilized in general clinical practice.

NR143 Thursday, May 10, 12 Noon-2:00 P.M.

NUCLEUS BASALIS NEURON LOSS IN SCHIZOPHRENIA

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Summary:

The nucleus basalis of Meynert (nbM) in the basal forebrain consists of cholinergic neurons that diffusely innervate the cerebral cortex. NbM neuronal loss has been associated with the dementia of Alzheimer's disease (AD), Parkinson disease, and Down's syndrome. Persistent cognitive deficits have been demonstrated in some patients with schizophrenia which some observers feel may reflect a dementing process. We hypothesized that there is cell loss in the nbM in cognitively impaired schizophrenic patients similar to that seen in AD.

We reviewed all autopsies performed at Saint Elizabeths Hospital over a four year period. By chart review three groups of patients were selected for neuropathologic study: patients who clinically appeared to have AD; schizophrenics (by DSM III criteria) with persistent cognitive deficits appearing early in their illness (S-D); and schizophrenics with no signs of significant cognitive deficits (S-ND). Specimens were taken from the nbM and from the frontal, temporal, and parietal cortex. Two neuropathologists, blind to diagnosis, independently performed cell counts in the mid-portion of the nbM and examined cortical sections for senile plaques.

Mean cell counts (per 500 um^2) in the nbM and ratings (on a scale of 0 to 3) for the presence of senile plaques in a pilot group of 10 patients were:

Diagnosis	Cell Count	Senile Plaques
AD (N=3)	27.7 ± 1.2	2.3 (range 2-3)
S-D (N=4)	47.5 ± 21.9	1.7 (range 1.2)
S-ND (N=3)	89.0 ± 3.6	0

A Kruskal-Wallis analysis of variance showed significant differences between the groups ($p < 0.01$). These preliminary data show evidence of nbM neuronal loss and plaque formation in a subgroup of schizophrenics similar to that reported in AD. A total of 23 cases (AD=5, S-D=11, S-ND=7) will be examined; and to control for between-group differences in age and gender, data from matched non-demented medical patients will be presented.

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EEG PHASE DIFFERENCES IN PSYCHIATRIC DISORDERS

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Summary:

Literature pertaining to lateralized electrophysiological distinctions among psychiatric groups indicates that, where significant differences are reported, the left hemisphere is more often involved in schizophrenics, and the right hemisphere is more often involved in depressives. The intent of this project was to investigate coherence and phase relationships of the EEG, both inter- and intrahemispherically, among schizophrenic, depressed, and borderline patient groups to provide more sensitive measures of cortical EEG activity.

Thirteen patients per group were selected from over 200 computerized records on the basis of singularity of diagnosis; homogeneity of medications; absence of substance abuse histories, where possible; and age range of 18-60 years. All the patients except one had clinically normal EEG evaluations. Inter- and intrahemispheric percent synchrony (SYN, requiring 80% coherence and phase angle $\pm 10^{o}$), percent coherence (COH), and percent power (POW), were computed for theta (5-8 Hz), alpha (9-12 Hz), and slow beta (13-17 Hz) from left and right bipolar temporal, central, and occipital leads during one minute of the eyes-closed, waking EEG obtained on admission.

The results indicate 1) significant increases in left temporo-central SYN and COH in schizophrenics; 2) significant right occipito-central increases in SYN and COH in depressives; 3) suggestive interhemispheric increases in SYN and COH in schizophrenics; and 4) no significant differences in left/right POW distributions.

The most important conclusion is that analyses of intrahemispheric coherence and phase-angle relationships significantly distinguished between patient groups, whereas, interhemispheric comparisons, percent power values, and the clinical EEG interpretations did not. The nature of the differences suggests distinctive functional organizations of cortical neurons between schizophrenics and depressives, and are consistent with previous studies indicating left-side involvement in schizophrenics and right-side involvement in depressives. Finally, based on earlier unpublished work suggesting increased SYN and COH during problem solving among normals, as well as theories of others hypothesizing over-activated left or right hemispheres in schizophrenics and depressives, respectfully, we tentatively deduce that SYN and COH measures may provide converging validation for speculations of lateralized EEG differences, and underscore the necessity for including them in future EEG investigations.

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LOCALIZED BRAIN ABNORMALITIES IN SCHIZOPHRENIA

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Summary:

Previous studies have identified a subtype of schizophrenia (called "negative" schizophrenia by Andreason, et al., 1982) that is associated with nonspecific evidence of brain abnormality such as enlarged cerebral ventricles and general neuropsychological deficits. Other research has indicated that schizophrenics, when considered as a unitary group, have some signs of localized brain disorder; and the left cerebral hemisphere has been implicated as the location of such disorder in studies using both CT-Scan densities and neuropsychological measures (Newlin, et al., 1981). The present study addressed the question of whether localized brain abnormalities can again be found in schizophrenia and whether these will be found only in the negative subtype of the disorder.

Three groups were drawn from a male inpatient population. Schizophrenics were subtyped by CT-Scan ventricle-to-brain ratios (VBR) to form two groups. Those with abnormally high VBRs were identified as negative schizophrenics and formed the HI-VBR group (n = 7). Other schizophrenics were designated for the NORMAL-VBR group (n = 29). The third group was comprised of adjustment or personality disorders (CONTROL group; n = 8). Dependent measures were indicators of localized brain abnormality derived from the CT-Scan (cerebral densities at 24 locations) and from the Luria-Nebraska Neuropsychological Battery (T-scores on ten localization scales). Currently available data were analyzed with multivariate analyses of covariance (with age, chronicity, and education as covariates). The anlysis of localized cerebral densities failed to show between group differences with simple density measures as well as with right-versus-left differences ($ps > .20$). The multivariate analysis of the Luria scales did indicate significant between group differences ($p < .03$), so subsequent univariate analyses of covariance were performed. Results indicated that the HI-VBR group performed more poorly than the other two groups on all of the localizing scales, with the difference reaching significance (at the .10 level) on five of the ten scales, including two left and three right hemisphere scales. The NORMAL-VBR and CONTROL groups did not differ significantly from each other on any of the scales.

These results did not support the hypothesis that strictly localized brain abnormalities would be found in HI-VBR schizophrenics. This study found no localized density abnormalities, and the neuropsychological dysfunction found in negative schizophrenics was bilateral and diffuse in nature. Previous neuropsychological studies suggesting left hemisphere deficits have been largely based on qualitative interpretation of performance; such interpretations must be questioned since empirically-based scales used here implicate both hemispheres.

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THE ELECTRORETINOGRAM IN SCHIZOPHRENIA

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Summary:

The search for evidence of brain dopamine hyperactivity in schizophrenia continues. One area of brain dopamine activity that remains relatively uncharted in schizophrenia is the retinal dopamine system. A potential tool to explore this system is the electroretinogram (ERG), an electrical potential elicited from the retina by a flash of light. The ERG has many components, the largest of which is the B wave. Since dopamine blocking agents (i.e., neuroleptics) decrease the amplitude of the b-wave in animals, we hypothesized that b-wave amplitude in schizophrenia might be increased.

METHODS: The subjects were 11 young RDC (+) inpatients with chronic schizophrenia withdrawn from medications for two weeks and 10 age-matched normal control volunteers.

After a half-hour period of dark adaptation each subject underwent the ERG procedure modified so that separate ERG's were obtained for different retinal photoreceptor cell types (i.e., rods, red-green cones, blue cones) by altering the colors of the light flashes or background. Values for normals and patients with schizophrenia were compared using the Mann-Whitney U test.

RESULTS: Blue cone b-wave amplitude was increased in schizophrenia at both flash intensities tested (low intensity flash, for patients with schizophrenia mean $\pm$ (SD) was 19.6 $\pm$ 9.1 microvolts and 6.9 $\pm$ 2.8 microvolts for normal controls, $p < 0.001$; high intensity flash, for patients with schizophrenia 25.9 $\pm$ 13.1 microvolts and 13.9 $\pm$ 7.8 microvolts for normals, $p < .04$).

In addition, there were significant ($p < .05$) elevations in the latency of the a-wave and the first oscillatory potential (OP) for ERGs of red-green cones, mixed rods and cones and all cone components.

In summary, blue cone b-wave amplitude may be increased in schizophrenia. This may be related to retinal dopaminergic hyperactivity or other factors. Hence, the ERG may provide a useful, non-invasive measure of retinal neurochemistry that is useful in schizophrenia and other neuropsychiatric disorders. Moreover, these findings may contribute to the further understanding of the role of neurochemistry in color vision. Studies are underway to attempt to replicate current findings.

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POSITRON EMISSION TOMOGRAPHY IN SCHIZOPHRENIA

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Summary:

Regional cerebral glucose metabolism utilizing positron emission tomography (PET) with ^{18}F-deoxyglucose (FDG) is a tool for the non-invasive three dimensional assessment of cerebral metabolism in man. Previous investigations with this technique suggest that frontal cortex glucose utilization may be depressed in patients with chronic schizophrenia, and that this frontal decrease ("hypofrontal pattern") correlates with decreased frontal cortex blood flow. We have investigated FDG utilization in chronic schizophrenic patients and in age and sex matched normal control subjects on the Donner 280-crystal tomograph (resolution 8mm full width at half maximum). Four male patients with chronic schizophrenia diagnosed by Research Diagnostic Criteria were unmedicated for at least two weeks prior to scanning. A matched scan was repeated in three of these patients at least two weeks after instituting neuroleptic medication treatment. Four normal control subjects were unmedicated and had no relevant medical or psychiatric history. Each subject received 3 -12 mCi of FDG with sampling of venous blood from a hand warmed in a water bath (44°C). The subjects were blindfolded and were given an auditory vigilance task to perform during the FDG uptake. Tomographic data were collected by matching PET scan levels to CT scan levels to obtain several slices including at least one midventricular-caudate slice.

Our analysis of these PET scans compares the ratio of frontal cortex to total hemisphere cortex in each individual by an automated procedure. The ratio in schizophrenic patients is lower than in normal controls, suggesting a tendency toward a "hypofrontal" pattern. Neuroleptic medications did not reverse this tendency to hypofrontality. Further quantitative analyses of regional cerebral FDG in unmedicated schizophrenics are shown in the figures and demonstrate that the pattern of regional cortical FDG utilization in schizophrenics was qualitatively different in both hemispheres compared to normal control subjects. Specifically, patients with chronic schizophrenia have relatively decreased bilateral prefrontal and perisylvian cortical FDG utilization, and relatively increased bilateral posterior temporal and occipital cortical FDG utilization compared to normal controls. These results suggest that patients with chronic schizophrenia have altered regional cerebral cortical glucose utilization which is distinguishable from normal controls and which cannot be explained by the effects of acute neuroleptic administration. These findings are consistent with cerebral blood flow studies (Ingvar et al.) and with earlier FDG PET scan studies (Buchsbaum et al.) showing a relative "hypofrontal pattern" of cerebral cortex functioning in chronic schizophrenia.

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FACIAL BEHAVIOR OF SCHIZOPHRENICS DURING INTERVIEW

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Summary:

This study applied ethological measurement techniques to schizophrenic facial behavior in an attempt to produce data free of preconceptualizations entailed by subjective rating scales of affect. Experimental subjects included 15 medication-free male inpatients meeting Research Diagnostic Criteria for schizophrenia, 6 paranoid and 9 non-paranoid. Control subjects included 12 medication-free male patients hospitalized for drug or alcohol abuse of comparable age, racial composition, and education. Each underwent a non-directive psychiatric interview performed by the senior author (RKP) with a videotape recording of the subject's face. Composite tapes were made of the first five minutes of each interview in mixed order. One of the co-investigators (BK) and another rater, both blind to subject identity, reviewed the video portions and scored facial behavior according to a system previously devised by BK which included 14 different types of facial movements. Numbers of words spoken by the subjects were counted from transcripts. Condensed mean results appear in the table:

ANOVA	Controls	Paranoids	Non-paranoids	F	P	Reliability
All facial movements	39.1	19.5	26.2	5.1	$<.05$	$r = 0.96$
Eyebrow movements	14.6	3.1	8.7	3.5	$<.05$	
Lower facial movements	18.1	12.7	15.7	1.0	n.s.	
# different movements	9.4	7.3	8.8	1.5	n.s.	
Words spoken	599.8	455.4	187.1	31.1	$<.01$	

Results indicate greater non-verbal and verbal expressivity of controls compared to schizophrenics. Especially intriguing was the double dissociation between non-verbal and verbal expression within the schizophrenics, paranoids showing much higher words spoken than non-paranoids but a drastic fall-off in facial movements, especially eyebrow movements. Ethologists have pointed to the role of eyebrow movements as signs of willingness for social contact, which may be diminished in the paranoids. Although the facial movements of the non-paranoids were greater in number than those of the paranoids, a great many of these appeared autistic.

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MODERN CRITERIA AND THE GENETICS OF SCHIZOPHRENIA

Miron Baron, M.D., New York State Psychiatric Institute, 722 West 168th Street, New York, NY 10032, Rhoda Gruen, M.A. (I), John Kane, M.D., Lauren Asnis, M.S. (I), New York, NY

Summary:

Genetic family studies offer a method of testing the validity of the distinction between "narrow" and "broad" schizophrenia. The relevance of narrowly defined diagnostic criteria to genetic research in schizophrenia was assessed in 84 nuclear families of schizophrenic probands. The study employed prospective proband selection; research diagnostic criteria; structured family interviews; blind, independent diagnoses of probands and relatives; assessment of putative schizophrenia "spectrum" disorders; and a control sample consisting of 90 families. The diagnosis of "narrow" schizophrenia was based on Taylor and Abrams criteria. The morbidity risk for "narrow" disease was significantly higher than the control rate (3.8% vs 0.3%). The overall rate of schizophrenia(including a "broader" illness form as defined by the Research Diagnostic Criteria) in the relatives of these patients was also significantly higher than the control risk (7.1% vs 0.6%), as was the rate of "spectrum" disorders, i.e., schizotypal and paranoid personality disorders (33.5% vs 11.2%). Relatives of patients with "narrow" illness form were at a greater risk for "narrow" schizophrenia, the total of "narrow" and "broader" schizophrenia, and the overall schizophrenia spectrum than relatives of schizophrenics who did not meet the "narrow" criteria. The data support the case for familial transmission of narrowly defined schizophrenia and suggest that "narrow" schizophrenia may be more severe genetically than "broad" schizophrenia.

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NEUROLEPTIC TREATMENT OF SCHIZOTYPAL PERSONALITIES

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Summary:

This study measures the response of patients with schizotypal personality disorder (SPD) to high potency, low dose neuroleptic medication. The DSM III designation of two groups of "borderline" personality disorder patients, one with schizophreniclike characteristics (schizotypal) and the other with unstable features (borderline) allows for evaluation of treatment responses in more clearly delimited patient groupings. Methods: Fourteen outpatients and six inpatients who satisfied DSM III SPD criteria were treated with low doses of Haloperidol (2 mgs. daily with buildup to 14 mgs. unless side effects intervened) for a period of six weeks after a two week placebo period. Assessment measures included the Schedule for Interviewing Borderlines, Global Assessment Scale, and Thought Disorder Index. Patients were evaluated at baseline and weekly thereafter. Results: Only 50% of patients were able to complete a full medication trial. Analysis of dropouts indicated high sensitivity to side effects (particularly akathesia and drowsiness) even at the 2mg.level and with availability of anticholinergics. Only 25% of patients tolerated even 10 mgs. of Haloperidol. Four patients subsequently given open trials of 5 to 10 mgs. of Thiothixene complained of similar side effects, particularly drowsiness. For purposes of data analysis, sixteen patients who were able to tolerate at least a two week medication trial were included. No placebo related improvement was noted. Significant on-drug improvement was noted on the SIB total schizotypal score and on the scales Ideas of Reference and Social Isolation. In contrast, the total SIB borderline score showed no change. GAS scores reflected significantly improved functioning. On the TDI there was a significant decrease in disordered responses on structured Verbal I.Q. tasks. Analysis of the subgroup of patients who completed the full medication trial showed no significant findings, but this may be due to a small sample size. Discussion: The results are consistent with Goldberg, et al (1983) and Serban (1983) and provide qualified support for positive response to low dose neuroleptic treatment in SPD. The finding that 50% of patients did not receive a complete medication trial is slightly in excess of the 40% dropout rate reported by Goldberg, et al (1983). In contrast to other recent studies, only patients meeting DSM III SPD criteria were included. This may have reduced the drug responsivity of the sample but allows more systematic evaluation of the "anti-schizotypal" effects of low dose neuroleptics. The study demonstrates the efficacy of low doses of neuroleptics with schizotypal patients while also highlighting the limited compliance in such a population.

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LONG TERM OUTCOME OF SCHIZOTYPAL PERSONALITIES

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Summary:

The first long-term follow-up of 28 DSMIII schizotypal personality (SP) inpatients has been completed as part of the Chestnut Lodge Follow-Up Study. Multi-dimensional outcome was assessed by interview 15 years (average) post-discharge (range 2-32 years). Each medical record was independently (i.e., blind to follow-up) abstracted for rediagnosis by current criteria and for multiple ratings of baseline (morbid and premorbid) sign and symptom, demographic and predictor variables. Only variables with acceptable interrater reliabilities were studied. SP outcome is compared with three other follow-up cohorts: Schizophrenia (S, n-163, DSMIII criteria), Unipolar Affective Disorder (UNI, n=44, DSMIII criteria), and Borderline Personality (BP, n=81, DSMIII and/or Gunderson criteria).

Admission diagnostic data demonstrate high overlap between SP and S as do baseline demographic and premorbid profiles. Follow-up data, however, demonstrate greater similarities between SP and the other two comparison groups (BP/UNI). Unlike S patients, SP's were living in less dependent circumstances, did not require highly structured further treatments, worked fulltime at fairly complex jobs and functioned reasonably despite their ongoing sign and symptom psychopathology. Only in social activity (frequency and closenes were SP's intermediate in outcome between S and BP/UNI. Long-term follow-up emphasized a distinctiveness between SP and S proper with SP becoming less a "variant" of S with time.

For SP as a whole, Global Functioning spread evenly across the range from poor to good thus rendering them more heterogeneous in outcome than any other diagnostic group. Representative case descriptions illustrate the range. Results support the elusiveness of SP as a specifiable and distinct diagnostic entity and suggest it covers a wide spectrum or group of disorders that will require further nosologic differentiation in the future.

Significance. These data represent a first contribution to the literature on the long-term course and outcome of a sample of patients with schizotypal personality as defined by current diagnostic criteria.

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SCHIZOTYPAL AND BORDERLINE PERSONALITY

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Summary:

The relationship between schizotypal personality disorder (SPD) and borderline personality disorder (BPD), two diagnoses that often overlap both conceptually and in clinical usage, was investigated, using the presence of other clinical characteristics, biologic markers, and family history as external validators in a study of hospitalized personality disordered (PD) patients. 22 patients clinically evaluated as having a primary DSM-III Axis II diagnosis were interviewed by two raters using the Structured Interview for the DSM-III Personality Disorders (SIDP) which also included an interview with an informant. Diagnosis was arrived at by consensus on the basis of the patient's and informant's response to the SIPD and the patient's behavior on the ward. Patients were also rated by two interviewers on the Diagnostic Interview for Borderline Patients (DIB) and the Schedule for Affective Disease and Schizophrenia (SADS). 18 of the 22 patients satisfied DSM-III criteria for either SPD or BPD, while 9 satisfied DSM-III criteria for both. The DIB criteria for BPD identified 7 of these 9 patients, but not patients with DSM-III diagnosis of either SPD or BPD without the other diagnosis.

When the DSM-III diagnosed non-BPD SPD patients were compared with the DSM-III diagnosed SPD with BPD (BPD-SPD) patients, the non-BPD SPD patients were significantly more likely to also meet DSM-III criteria for compulsive personality disorder ($p < .05$, Fisher's Exact) while the BPD-SPD patients were more likely to have met RDC and DSM-III criteria for major depressive disorder (MDD) retrospectively at admission ($p < .05$, Fisher's Exact). Preliminary data suggest that family history of affective disorder may be more prevalent in the BPD-SPD patients.

Abnormality of smooth pursuit eye movements (SPEM), is observed in schizophrenics, affectively ill patients, and volunteers with SPD, although the patterns may differ between diagnostic groups. In our sample, non-BPD SPD patients were significantly more likely to show consistently poor tracking (p .05, Fisher's Exact) sometimes in a spikey pattern characteristic of schizophrenics while BPD-SPD patients were significantly more likely to show variable tracking in a saccadicly disrupted pattern, similar to that observed in affective patients. Although these results are preliminary, they raise the possibility that non-BPD SPD patients may constitute a separable group from BPD-SPD patients, with the former more related to schizophrenia, and the latter to a disorder of affective instability with both groups sharing a tendency to psychotic-like symptoms.

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PLASMA SERINE AND PSYCHOTIC SYMPTOMATOLOGY

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Summary:

Elevated plasma serine and serine/cysteine (S/C) ratios have been reported in psychotic patients (Waziri et al., 1983). In an attempt to clarify whether specific psychotic symptoms were correlated with the elevated S/C ratios, approximately 140 charts selected from consecutive admissions to the University of Iowa Psychiatric Hospital during 1982 were reviewed blindly in regard to their S/C ratio. Six psychotic symptoms were rated as either positive or negative if reported within 48 hours of the blood drawing for plasma amino acid profile. These six symptoms were: paranoid delusions, hallucinations, other delusions, bizarre behavior, agitation, formal thought disorder. The presence or absence of symptoms were based on reviewing clearly described mental status examinations in progress notes and nurses notes. Diagnosis was made according to the criteria of DSM-III using all the clinical chart material. All blood samples for fasting amino-acid profiles were drawn at 7:30 a.m.

Seventy-seven charts had clear unambiguous diagnoses and sufficiently detailed clinical notes for inclusion in the study. Twenty-five patients had schizophrenia, schizoaffective, paranoid disorder or schizophreniform disorder; 15 had bipolar affective disorder, mania; 15 had depressive diagnoses; 22 had other diagnoses. The number of psychotic symptoms correlated with the S/C ratio. Of the 6 psychotic symptoms, paranoid delusions, other delusions, bizarre behavior and formal thought disorder were positively correlated with the S/C ratio; whereas agitation weakly correlated and hallucinations were negatively correlated with the S/C ratio. The best predictor of an elevated S/C was paranoid delusions; the best two predictors were paranoid delusions and bizarre behavior; the best three were paranoid delusions, bizarre behavior and formal thought disorder. The patients were divided in psychotic vs. nonpsychotic. The psychiatric diagnosis did not correlate with the S/C ratio in the psychotic patients; whereas in the nonpsychotic patients, the psychiatric diagnosis did correlate with the S/C. The patients with schizophrenia who had no active psychotic symptoms had a mean serine level (SL) of 18 mg/dl which is elevated; nonpsychotic bipolar affective disorder patients had a mean SL score of 14 mg/dl which was borderline; and nonpsychotic patients with other affective disorders had a mean SL of 12 mg/dl which was similar to SL in nonpatient controls.

NR154 Thursday, May 10, 12 Noon-2:00 P.M.

ONE-CARBON (METHYL, CH3) METABOLISM IN SCHIZOPHRENIA AND MOOD DISORDERS

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Summary:

One-carbon (Methyl,CH_3) metabolism abnormalities have been thought to occur as biological correlates of major psychiatric disorders. Previous results from our laboratory have indicated decreased activity (Vmax) of the enzyme methionine adensoyltransferase (MAT) in erythrocytes of medicated schizophrenic patients compared to normal subjects. We presently report on significant differences in CH_3 metabolism parameters of schizophrenic and affective disorder patients , and on distinct medication-induced changes of this specific type of metabolic activity, in the same diagnostic groups.

To determine whether or not similar abnormalities in one-carbon metabolism could be found in different diagnostic populations, we assayed erythrocyte samples from 15 manic and 10 depressed patients, diagnosed according to DSM-III criteria. We have found that manic subjects have MAT Vmax's significantly higher ($p<0.023$,Mann-Whitney), and depressed subjects have Vmax's significantly lower than normals ($p<0.0048$); the latter finding is similar to that seen previously in schizophrenic patients. Additionally, levels of the phospholipid phosphatidylcholine (PC) measured in erythrocyte membranes (RBC's) show a clustering in the low range for the depressives, and in the high range for the manics.

To evaluate the effects of psychotropic medications on erythrocyte MAT and phospholipids we collected paired blood samples from 10 schizophrenic and 5 manic patients: the first sample was drawn from unmedicated patients immediately upon admission; the second, after psychotropic medication (neuroleptics for schizophrenics and lithium for manics) was begun. In the schizophrenic subjects, the MAT Vmax significantly increases after medication, tending to approach the normal range, whereas in manic subjects, lithium treatment is associated with a decrease in the Vmax values which show, again, a tendency to return to normal levels. At the same time, the percentages of PC in the RBC membranes, measured in the same patients, tend to change in a manner that reflects the Vmax changes: increasing with neuroleptics, and decreasing with lithium, thus suggesting that the changes in enzyme activity may be modulating phospholipid composition.

The results suggest that one-carbon metabolism appears significantly decreased in schizophrenics and depressives and significantly elevated in manics. These findings may have clinical and diagnostic implications, in the light of some overlapping features between schizophrenia and mood disorders. Only the joint efforts of phenomenologically and nosologically minded psychiatrists and basic neuroscientists can clarify these issues. On the other hand, it appears that neuroleptic and/or lithium therapy may actually minimize rather than being the source of the differences in MAT activity seen in schizophrenic and manic patients. The question of the possible relationship between these molecular medication effects and the clinical efficacy of the psychotropics also awaits further investigations.

NR155 Thursday, May 10, 12 Noon-2:00 P.M.

NEUROENDOCRINOLOGY OF NEVER MEDICATED TREATED SCHIZOPHRENICS

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Summary:

Cleghorn, Brown et al. (1982; 1983) have found that schizophrenics (a few of them never medicated) showed a marked GH response to a low dose of apomorphine. This preliminary data can be interpreted as the first in vivo demonstration of the supersensitivity of dopamine receptors and related structures in schizophrenia. The aim of this study was to carry out a similar investigation in additional cases of schizophrenics who have never been treated.

Eleven newly admitted, physically healthy, young, male schizophrenics, who have met the RDC for schizophrenia were included in the study. The peak value of the GH responses to 0.25 mg apomorphine sc. showed a greater variablity in schizophrenics, than in the controls. None of the controls, but five out of the 11 schizophrenics showed a greater than 5.5 ng/ml GH peak value. There was no difference in the symptom profile (positive versus negative symptoms) between the schizophrenics who showed and who did not show the GH response. The GH response did not correlate with the base-line GH, cortisol or DBH values. Schizophrenics had significantly lower serum prolactin levels than the controls both before and after the apomorphine administration, however, the prolactin decrease after apomorphine was similar in the two groups. The schizophrenics had lower base-line serum DBH activity than controls. In the controls apomorphine induced a significant increase of serum DBH activity, whereas in schizophrenics there was no consistent change, which seems to suggest that serum DBH activity may be related to dopaminergic functions.

In conclusion, our findings support the dopamine theory of schizophrenia. Schizophrenics who had never been medicated (1) show more frequent GH response to small doses of apomorphine than matched healthy controls, (2) present lower prolactin levels than healthy controls, (3) lack the significant change of serum DBH activity after apomorphine, found in healthy controls.

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NOREPINEPHRINE DYSFUNCTION IN SCHIZOPHRENIA

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Summary:

Introduction: Elevated norepinephrine (NE) has been found in postmortem brain tissue and cerebrospinal fluid (CSF) in paranoid schizophrenia compared with control specimens. NE metabolites have been found to vary with clinical state in bipolar affective and anxiety disorders. Furthermore, clinical observations have found severe mania and acute psychosis to be virtually indistinguishable, suggesting a common neurobiology during these episodes. The purpose of the present study was to test the effect of clinical state and schizophrenic subtype on the plasma NE metabolite,3-methoxy-4-hydroxyphenylglycol (MHPG).

Methods: Fifteen individuals diagnosed by research diagnostic criteria and subtyped by DSM III criteria as paranoid or undifferentiated were invited to participate in studies at NIMH wards at Saint Elizabeths Hospital. Twice daily BPRS ratings were performed by a staff unaware of the patient's medication status. Patients were medication free for a minimum of two weeks prior to participation in this study. Plasmas or serums which had been obtained by venipuncture at 8:00 a.m. twice weekly were selected for MHPG assays according to peaks and valleys in longitudinal BPRS ratings. Samples were stored at -40°C until assayed blindly using gas chromatography-mass spectrometry. Twenty-one normal control samples collected in another study were used for comparison.

Results: For patients with undifferentiated schizophrenia, plasma MHPG was significantly elevated in the high psychotic state (4.0 $\pm$ 0.32 ng/ml) in comparison to the low psychotic state (2.9 $\pm$ 0.21 ng/ml, $p < 0.05$). The paranoid subgroup MHPG did not differ with respect to clinical state. A correlation was found between change in total BPRS score and change in MHPG concentration for all patients taken as a group. The mean for the normal group was 3.0 $\pm$ 0.5. Other data to be presented will be the effect of chronic clonidine in conjunction with neuroleptics on BPRS symptoms, as well as ^{3}H paramino clonidine binding in postmortem schizophrenic brains and normal controls.

Discussion: The present study supports other evidence for NE dysfunction in paranoid vs undifferentiated schizophrenia. Clinical state accounts for some of the variance in plasma MHPG concentrations in undifferentiated schizophrenia. The lack of state related change in the paranoid subgroup may reflect a constant state of hypervigilance in these individuals. Future studies of MHPG in plasma, urine and CSF of schizophrenic individuals may benefit from attempts to control for clinical state as a source of variance when comparing this group to normal controls. Plasma MHPG provides a relatively risk free means by which to monitor state related alterations in sympathetic activation associated with psychosis.

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DOPAMINE FUNCTIONAL SUBTYPES OF SCHIZOPHRENIA

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Summary:

The present studies suggest that dopamine (DA) activity in schizophrenic patients may be seen as a continuum. One end of the continuum is characterized by high DA release while the other end is characterized by DA receptor supersensitivity. Postsynaptic DA feedback mechanisms appear intact in schizophrenia as patients with high DA release demonstrate DA receptor subsensitivity. Conversely, patients with low DA release demonstrate DA receptor supersensitivity. Further, these two subtypes of schizophrenia appear characterized by different clinical presentations.

Twenty consenting inpatients presenting with RDC schizophrenia underwent a ten day drug-free period at the end of which DA release was determined. 10 cc of CSF was withdrawn by lumbar puncture and the levels of the major DA metabolite-homovanillic acid (HVA) were determined from the last CSF fraction (8 to 10 ml) by HPLC with electrochemical detection. DA receptor sensitivity was assessed by measuring a postsynaptic event, release of growth hormone (GH) following DA receptor stimulation by apomorphine. Patients received 0.75 mg of apomorphine (s.c.) with serial blood samples drawn at -30, -15, 0, 40, 50, 60, 70 and 80 minute intervals via an indwelling venous catheter for plasma GH levels determined by radioimmunoassay. Patient psychopathology was assessed with the New Haven Schizophrenic Index. A clear inverse relationship between DA release (HVA levels) and DA receptor sensitivity (apomorphine-peak GH response) was seen. The relationship of HVA to GH was best described by a quadratic equation ($F=81.34$, $df=3,17$, $p<0.0001$) where $HVA=146-2.94GH+0.027GH^2$ with HVA and GH levels both expressed in ng/ml. This equation accounted for 83% of the variation in GH and HVA levels, and suggested that the DA systems in these patients could be characterized as demonstrating DA receptor supersensitivity (high GH-low HVA) or high DA release (low GH-high HVA). Analysis of patient symptoms (NHSI) suggested that patients demonstrating a DA receptor supersensitivity were characterized by an unusually high incidence of both formal thought disorder ($t=2.27$, $df=72$, $p<0.03$) and stuporous catatonia ($t=2.13$, $df=72$, $p<0.04$).

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LOWER CSF DYNORPHIN IN SCHIZOPHRENIC PATIENTS

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Summary:

Dynorphin is a very potent neuropeptide recently isolated from the brain and pituitary. Using a highly specific and sensitive radioimmunoassay (IC 50 of 7 fm/assay tube), we measured CSF dynorphin$_{1-8}$ concentrations in 25 first-break Chinese schizophrenic patients and in 25 Chinese neurological controls. All patients met DSM-III criteria for schizophrenia or schizophreniform disorder and were free of neuroleptic drugs for at least one week prior to the collection of CSF. The control group studied in parallel consisted of patients with neurological illness such as peripheral neuritis, arthrosis, myelopathy and tumor. All CSF was collected under a standardized protocol into tubes containing the protease inhibitor aprotinin and immediately frozen on dry ice. Only CSF samples with normal protein, chloride, glucose and no cells were assayed. The CSF dynorphin$_{1-8}$ concentration in schizophrenic patients with significantly lower than that of the neurological controls (108 $\pm$ 5.3 fm/ml and 144.6 $\pm$ 6.8 fm/ml respectively, p 0.001). Classical kappa opiate agonists induce psychtomimetic effects. The amount of dynorphin$_{1-8}$ that reaches the spinal fluid should be inversely proportional to the rate of utilization. Our data are consistent with an alternation in the dynamiCs of dynorphin$_{1-8}$ in schizophrenia.

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CSF CORTICOTROPIN RELEASING FACTOR IN NEUROPSYCHIATRIC DISEASE

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Summary:

Corticotropin releasing factor (CRF) was analyzed in the cerebrospinal fluid (CSF) of 60 patients with a diagnosis of schizophrenia (n=26), major depression (n=9), Alzheimer's disease (AD) (n=19), or normal controls (n=6). CRF, MHPG, HVA, and 5-HIAA were assayed in the CSF samples of all the populations. Lumbar punctures were performed at 0900 in AD and depressive patients and 1400 in schizophrenics and normals. In addition, data was available from a standard dexamethasone suppression test (DST) in the depressives and many of the AD patients. Mean nocturnal cortisol concentrations were also determined in AD. Following a 1-hour habituation to an intravenous catheter, bloods were drawn every 30 minutes from 2100 to 1200. Neither age, sex, nor weight were significant covariants of CRF concentrations. One-way ANOVA indicated no differences between CRF concentrations and diagnostic group. Similarly, within each diagnostic group, CRF concentrations did not correlate with the severity of symptoms, as assessed by the BPRS, Hamilton and Blessed Scales. A significant inverse relationship existed between CSF MHPG and CRF concentrations in schizophrenics ($r=-.51$, $p=.02$, $n=20$), that seemed to be present in normal controls as well ($r=-.74$, $p=.06$, $n=7$). In the AD patients a nonsignificant inverse correlation between MHPG and CRF was also present. However, depressives, rather than following the pattern of the other study populations, displayed a positive relationship between CRF and MHPG ($r=.60$, $p=.07$, $n=10$). These data suggest that what may be a normal tonic inhibitory relationship between noradrenergic activity and CRF, may be lost in depressives. Cortisol concentrations, either before or after dexamethasone in depressives or AD, did not significantly correlate with CRF. Dexamethasone suppressors and nonsuppressors could not be differentiated by CSF CRF concentrations. Similarly, no relationship between mean nocturnal cortisol and CRF concentrations was discerned.

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PROSTAGLANDIN E2 IN SCHIZOPHRENIC AND MANIC PATIENTS

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Summary:

Metabolic products of arachidonic acid "prostaglandins" (PGs), in particular PGE2, interact with neurotransmitters and modulate the release of pituitary hormones. While PGs play a variety of roles in the normal CNS, changes in the release of PGs and/or in their effects have not been clearly established in CNS disorders. Both a PGE2 increase and a decrease have been hypothesized to be of significance in the etiology of schizophrenia. However, experimental evidence thus far is inconsistent.

In order to further study possible PG changes in schizophrenia and explore their relationship to psychotic state and psychotropic medication, PGs were measured in patient and control groups. Subjects with significant medical diseases and substance abuse were excluded from the study. The diagnostic groups, according to DSM-III, were: (1) Schizophrenic disorder with acute exacerbation, (2) Schizophreniform disorder, (3) Major affective disorder, manic episode, (4) Healthy controls, and (5) Migraine patients. The groups were matched for age and sex. All subjects were drug-free for at least 14 days preceding the experiment. After overnight fasting, venous blood was obtained between 8-10 am. The maximal plasma sample storage time was 6 months at -70°C and all the samples were analyzed in the same RIA. PGE2 was assessed by measuring its main plasma metabolite 15-keto-13,14-dihydro-PGE2. The essence of the determination is conversion of the metabolite to its stable bicyclic product which is then measured by a specific RIA.

Results: mean±SE plasma PGE2 metabolite levels (picog/ml) were: 132±7(n=9), 148±14(n=7), 138±21(n=9), 55±40(n=7), and 53±12(n=15) for the schizophrenic, schizophreniform, manic, healthy and migraine group, respectively. Within each group, there were no differences between patients treated prior to the washout period with neuroleptics and/or lithium and non-treated patients. The length of drug-free period also did not correlate to the PG plasma levels.

The results indicate that PGE2 production may be increased in acutely symptomatic schizophrenic, schizophreniform and manic patients. It seems plausible to assume that either the psychotic state per se, or factors such as anxiety and motor activity, or "stress", and perhaps others, can affect PGs. These - previously unexplored - areas of PG research are currently being investigated.

NR161 Thursday, May 10, 12 Noon-2:00 P.M.

THE METYRAPONE TEST IN MAJOR PSYCHIATRIC DISORDERS

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Summary:

Utilizing neuroendocrine assays such as the dexamethasone suppression test (DST) to examine the major psychiatric disorders has received considerable attention in psychiatric research. This study is an attempt to extend the potential of laboratory tests in psychiatry.

The single dose metyrapone test (MT), a useful procedure for assessing the integrity of the hypothalmic-pituitary-adrenal (HPA) axis, has not previously been applied to psychiatric disorders. Metyrapone inhibits adrenal 11-beta-hydroxylase, which normally converts cortexolone (11-deoxycortisol) to cortisol. The MT was originally developed to detect hypofunctioning of the HPA axis such as that found in Addison's Disease. The MT may also thus be of value in further assessing psychiatric disorders where neuroendocrine dysfunction is suspected.

Sixty-nine patients admitted to the Buffalo VA Medical Center or the Erie County Medical Center were included in this study. All patients were between 18 and 65, provided valid informed consent, were free of endocrine and other medical illnesses, weren't exposed to any drugs known to interfere with neuroendocrine testing, and had no history of substance abuse. All subjects were interviewed utilizing the Schedule for Affective Disorders and Schizophrenia (SADS), and were determined to meet DSM-III criteria for either major depression (35 cases), mania (10 cases) or schizophrenia (24 cases). Eligible subjects had baseline bloods drawn at 8 AM and 4 PM and were then administered a weight-adjusted dose (2-3 gm.) of metyrapone at midnight. The next day bloods were drawn at 8 AM and 4 PM for plasma-cortisol, cortexolone, and metyrapone levels. All bloods were immediately refrigerated and analyzed utilizing high performance liquid chromatography. A DST was completed 48 hours later on 51 subjects. Twenty-five normal volunteers also completed the MT, but not the DST, on an outpatient basis.

MT results were considered abnormally low when cortexolone values were lower than 7 ug/dl. Preliminary data indicated that MT abnormalities were found in 4 patients with major depression (11%), 1 patient with mania (10%), and 5 patients with schizophrenia (21%). These initial findings provide some evidence for HPA axis hypoactivity, but this does not appear specific for any diagnostic group. All 25 controls had normal MT results. The DST data gathered in this study also suggested non-specificity, in that 6 of 12 (50%) of the schizophrenics as well as 12 of 33 (37%) of the depressives and 4 of 6 (67%) of the manics tested were non-suppressors. This study, like many recent reports on the DST, suggests that HPA axis dysregulation may not be diagnostically specific in psychiatry, and does not support the routine use of the MT in psychiatric clinical practice.

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CARBIDOPA, DEXAMETHASONE EFFECT AND PINEAL INDOLES

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Summary:

Both serotonin (5HT) and melatonin (MT) involvement in hypothalamic-pituitary-adrenal (HPA) regulation has been suggested. As 5HT is the substrate for MT synthesis, 5HT depletion can result in decreased formation of MT. Consequently, it is important to differentiate between the effects of MT and 5HT depletion. We tried to distinguish the MT from 5HT effects on HPA by reproducing the 5HT dependent decrease of MT synthesis without a simultaneous decrease of 5HT in the hypothalamus. Considering that the pineal body is located outside the blood-brain barrier (BBB), the 5HT synthesis inhibitor-carbidopa (carbidopa does not penetrate the BBB) has been used for the selective decrease of pineal 5HT synthesis. 5HT metabolites in brain tissues were determined by a HPLC procedure.

Carbidopa (50 mg/kg i.p.) decreased pineal 5HT and 5HIAA by 100 percent and increased pineal tryptophan content by 100 percent. There were no changes in 5HT metabolites in the hypothalamus.

In normal human volunteers carbidopa administration (75 mg/day, 3 days) did not change serum cortisol suppression by dexamethasone (DEX). The data suggests 5HT rather than MT involvement in HPA response to DEX.

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CARBAMAZEPINE IN NORMAL EEG VIOLENT PSYCHOTICS

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Summary:

Carbamazepine is useful in the treatment of violent psychotic patients with EEG abnormalities. It is not known if it would help similar patients with normal EEGs. I therefore identified violent patients who had received carbamazepine as an adjunct to neuroleptics, had a normal clinical EEG and without an affective disorder. There were 7 patients (5 males: mean age 35 ± 8.8, mean length of hospitalization 11.6 ± 4.2 years). Because of an administrative decision to discontinue the psychotropic use of carbamazepine, it was possible to study three 6-week periods (immediately before carbamazepine, before discontinuation, and immediately after discontinuation). There was a significant difference amongst the three periods in the frequency of aggressive episodes ($F(2,6)=11.32, p<0.01$). The mean (±SD) number of aggressive episodes during the carbamazepine period (1.14±1.21) was significantly less than that either before (3.14±2.27: Scheffe test, $p<0.002$) or after (3.00±.91: Scheffe test, $p<0.02$) carbamazepine treatment. To determine whether this antiaggressive effect was greater in patients with EEG abnormalities, I have recently examined episodes of aggression in the six weeks before and last 6 weeks of carbamazepine treatment in 11 patients with normal EEGs (7 male, mean age, 31±8 years, mean length of hospitalization 8.6±5.9 years) and 8 patients with abnormal EEG's (6 male, mean age 36 ± 12 years, mean length of hospitalization, 11.0±15.1 years). A two-way ANOVA (EEG x treatment) indicated a significant treatment effect ($F(1,18)=18.5, p=.0004$), with a decrease in episodes of aggression from pretreatment to treatment in both the normal EEG (2.6± 2.0 vs 1.2±1.2) and the abnormal EEG group (2.4±1.2 vs 1.5±1.7). There was no significant EEG group effect ($F(1,18)=2.6, p=.12$, N.S.), and examination of the results suggests, if anythi-g, a trend for normal EEG patients to show the greater improvement. These findings raise the possibility that carbamazepine's antiaggressive effect may not be related to an anticonvulsant action.

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ALCOHOLISM IN SCHIZOPHRENIC INPATIENTS

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Summary:

Both clinical experience and limited research indicate alcohol abuse is a major problem in schizophrenia. Among the difficulties in this area are a lack of systematic studies and an unavailability of screening instruments validated for this population. With this in mind, we evaluated within 48 hours forty-one consecutively admitted DSM-III diagnosed schizophrenic patients. They were given the Michigan Alcoholism Screening Test (MAST); an alcohol and drug history was taken; and a Brief Psychiatric Rating Scale was completed by a psychiatrist. Using a MAST score ≥ 5, 73% fulfilled criteria for definite alcoholism. Ten items accounted for 93% variance on the original 25-item questionnaire. In support of the validity of the MAST scores, individual response patterns did not show response biases. Correlations among MAST scores, alcohol use histories, and psychopathology will also be analysed. Specific MAST item responses revealed: 1) amnestic "blackouts" in 59% of patients; 2) assaultive behavior or arrests for drinking related incidents in 44%; 3) liver disease attributed to alcohol in 17%; 4) an alcoholic parent in 51%. Additional sociodemographic and psychiatric characteristics of alcoholic and of non-alcoholic schizophrenics will be compared. This study supports the clinical observation that alcoholism is a significant problem in schizophrenia, with potential effects on patient management and pharmacotherapeutic intervention. Furthermore, the abbreviated 10-item MAST appears to be a valid screening tool to identify this inpatient problem.

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CT PERIVENTRICULAR LUCENCIES IN SENILE DEMENTIA ALZHEIMER TYPE AND MULTI INFARCT DEMENTIA

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Summary:

Although the C-T scan has become an indispensable tool for studying the brain and brain diseases, it has not yet proven to be useful in studying or diagnosing most of the primary dementias. Cerebral atrophy, ventricular dilation and parenchymal density are more related to aging than to the diseases causing the dementia. In our clinic, for the diagnosis and treatment of dementia, we reviewed 349 C-T scans particularly looking for the presence of periventricular lucent areas. This finding has only been mentioned in the literature, but never completely studied.

Our sample consisted of the following groups; young normals (n=35) elderly normals (n=101) Alzheimer's types (160) and vascular type of dementia (n=53). Overt infarctions were found in 0% of the young and 5% of the elderly normals, 4% of the Alzheimer's types and 17% of the vascular type. Periventricular lucencies were found in 0% of the young 12% of the elderly normals, 27% of the Alzheimer's types and 49% of the vascular types. The clinical findings of the patients with and without lucencies were compared and there was no significant correlation with stroke history, hypertension, diabetes, obesity, vertigo syncope, focal neurological signs or extrapyramidal system disorder. There was a significant correlation between the presence of lucencies and gait disturbance. The presence of lucencies increased with increasing age. Only 4% of the patients under the age of 65 have periventricular lucencies (excluding the vascular dementia group), 23% of the patients between 65-75 yrs. old had lucencies and 40% of the patients over the age of 75 have lucencies.

The significance of these findings need to be clarified. Other investigators have commented on "hypodense regions" and found that a similar number of Alzheimer's type patients have them, however they have not been described as periventricular. Binswanger's disease is noted for white matter lesions, however our patients did not exhibit hypertension and Binswanger's disease is described as rare, which was not the case in our lucent sample. Aside from infarctions as an explanation two other hypotheses will be explored; the role of ischemia in these patients and the role of normal pressure hydrocephalus.

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NORMAL CT SCAN IN THE ELDERLY: A FOLLOW-UP STUDY

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Summary:

A population of 50 fit volunteers, over the age of 60, were first interviewed, psychometrically tested and CT scanned. The group was followed up after two to four years and the procedures repeated. This study apparently forms the first reported CT scan and psychometric follow-up of a fit elderly population.

At follow-up, ventricular size was related to a general score of memory and to new verbal learning. Psychometric test results correlated well with each other except for a paired associate learning test. None of the CT measures were related to age. Frontal brain densities related to ventricular size but not to other regional brain densities, although all the non-frontal densities related well to each other.

Changes between initial and follow-up times were then assessed. Psychometric and CT results remained remarkably stable, however a small sub-group (10%) emerged who showed reduction in psychometric scores, an increase in ventricular size and lower left thalamic brain densities. Initial "cortical atrophy" predicted larger ventricles at follow-up but not cognitive deterioration. Indeed, no initial CT scores were good predictors of cognitive deterioration. Initial brain density scores had greater predictive value for future ventricular size and cognitive score than did "cortical atrophy", indicating that "cortical atrophy" may be a misnomer for sulcal widening. Nine percent of subjects had suffered a first depressive episode and this sub-group had significantly larger ventricles, both initially and at follow-up. Twelve per cent of subjects had suffered a recent death of spouse and this sub-group had significantly larger ventricles at follow-up.

Results suggest that, in the elderly, there is no reason to expect a deterioration in cognitive abilities or CT scan results unless a disease process is occurring. Such a process may be indicated by subtle cognitive deterioration or by late onset depressive illness, both of which are associated with ventricular enlargement.

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ORAL PHYSOSTIGMINE IN SENILE DEMENTIA ALZHEIMER TYPE: A TWO PHASE STUDY

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Summary:

There is increasing evidence that the memory deficits in Senile Dementia of the Alzheimer Type (SDAT) are related in part to a functional deficit in acetylcholine. While attempts to improve memory in these patients with acetylcholine precursers have been unsuccessful, there have been reports of some patients improving after acute oral or intravenuous treatment with physostigmine, an acetylcholinesterase inhibitor. These promising results raise the question of whether physostigmine can feasibly be given orally on a longer term continuous basis, and whether an effective dose can be predicted by response to short-term treatment. Further questions include the possibility that physostigmine might induce depression in elderly patients, as reported in younger normal subjects, and possible circulatory problems. We have therefore investigated response to oral physostigmine in patients with SDAT in a two-phase study. The first phase involved short-term treatment with placebo and each of three dose levels in double-blind, randomized order, for four successive two-day trials. This was followed by a three-week open trial on the dose that produced best response in the first phase. Seven out of eight patients improved in memory performance on the Buschke Selective Reminding Test on at least one dose level. In each case, the best performance was on the highest dose tolerated, which was generally 2 mg. Of these patients, six maintained or increased their improvement during three weeks of treatment. The two patients not responding to the three-week treatment were the most and the least severely impaired patients in the group. Physostigmine at these doses was generally well tolerated. The commonest side effect was nausea at 2 mg. in two of the patients and at lower doses by one. There were no episodes of bradycardia or hypotension. One patient developed a dose related mild increase in depressed mood during the initial short-term treatment period but not during the three-week period. On the other hand, two patients became euphoric during the long-term treatment period; neither had a previous history of mania, hypomania, or depression. Three patients had episodes of increased blood pressure and tachycardia. These results show that it is feasible to give physostigmine orally over relatively longer periods of time in elderly patients with SDAT, and that short-term response predicts response at least to subacute treatment.

NR168 Thursday, May 10, 12 Noon-2:00 P.M.

A STUDY OF FAMILIAL ALZHEIMER'S DISEASE

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Summary:

At present, the role of genetic factors in Alzheimer's Disease and senile dementia of the Alzheimer type (AD/SDAT) is not clear. The prevalence of the familial form of this disorder has not been determined and whether it differs phenomenologically or in terms of clinical course from the sporadic form of the illness remains unclear. To investigate these questions, family histories were obtained for probands with clinically diagnosed AD/SDAT, nondemented controls and other psychiatric controls seen in research studies conducted at the Bronx VA Medical Center. To enhance correct ascertainment, two family members for each proband were interviewed using a structured format. A familial case of AD/SDAT was defined as any patient with either a first or a second degree relative meeting operationally defined criteria for progressive dementia without other psychiatric or neurologic disease. The percent of familial cases among AD/SDAT probands was 46% compared with <10% in both control groups. Within the AD/SDAT group, the mean age of onset was significantly younger for familial than for nonfamilial cases (52.8 yrs. vs. 65.3 yrs., respectively). Symptoms were assessed with subscales of the Alzheimer's Disease Assessment Scale (Rosen, Mohs and Davis, Am. J. Psychiat. 1984, in press). Familial cases had more severe cognitive impairment than nonfamilial cases on this scale with mean scores of 60.8 and 30.4, respectively. Subscale analysis revealed that the most marked difference between groups was on the language subscale such that familial patients had more severe impairment than nonfamilial patients (17.3 vs. 8.9, respectively). Differences on memory, praxis and behavioral subscales were less pronounced. Longitudinal follow-up data for up to two years on these patients are now being analyzed to determine whether the rate of decline differentiates these two groups.

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CSF ACETYLCHOLINESTERASE IN DEMENTIA SYNDROMES

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Summary:

CSF Acetylcholinesterase (AChE) activity determinations were made using a radioenzymatic assay in thirty-six patients. This included twelve patients with the definite clinical diagnosis of senile dementia of the Alzheimer's type (SDAT/AD), twelve with possible SDAT or other dementing illness, and twelve age-matched controls. AChE activity was determined in forty-seven additional patients undergoing myelography whose ages ranged from twenty to eighty-five. Using data from these latter patients, an age curve was determined for CSF AChE activity; AChE increases with age according to the formula $Y = 0.19X + 3.94$. Patients with the definite clinical diagnosis of SDAT/AD had significantly lower CSF AChE activity than patients with early or other types of dementing illness. ($P < .05$) When compared with age-matched controls, AChE activity in the SDAT/AD group was also significantly lower. ($P < .05$) These data suggest that while AChE activity may not be useful as a presymptomatic test for SDAT/AD or indeed in those patients with very mild symptoms, it may be useful in confirming the diagnosis in mild to moderate cases and as a research tool in epidemiologic and pharmacologic studies.

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NORTRIPTYLINE TREATMENT OF POST STROKE DEPRESSION

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Summary:

Thirty-four patients with post-stroke depression were entered in a randomized, double-blind study analyzing the efficacy of the antidepressant nortriptyline in the treatment of this mood disorder. Nortriptyline treated patients (N=14) and placebo treated patients (N=20) were similar in terms of demographic variables, time since stroke, cognitive impairment, impairment in activities of daily living, neurological examination findings, and CT scan determined brain lesion size and location. Half of the patients in each group had the symptom cluster of major depression by DSM III criteria. Patients treated with nortriptyline showed significantly greater improvement in their depression compared to placebo treated patients as measured by the Hamilton Depression Scale ($p=.006$), Zung Depression Scale ($p=.027$), Present State Examination ($p=.062$), and an Overall Depression Scale ($p=.008$). Successfully treated patients had serum nortriptyline levels that were in the same range as that found to be useful for the treatment of functional depressions. Since our previous work has shown that post-stroke depressions are common (30%-60% of acute and chronic post-stroke patients), severe (often fulfill the criteria for major depression), longstanding (last greater than 6 months), and are rarely treated, the demonstrated efficacy of nortriptyline provides a significant addition to the treatments available for stroke patients.

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APOMORPHINE AND ALCOHOLISM

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Summary:

The effects of apomorphine on the manifestations of alcohol dependence and on the prolactin response have been studied in 27 male alcoholic volunteers aged between 20 and 55. Serum prolactin was measured before and after administration of apomorphine by radio-immune assay. None of the patients had liver cirrhosis or was taking any other drugs. All subjects were the participants of the regular rehabilitation program (counseling, group discussions). The control group, which was exposed only to counseling and group discussions, comprised of 27 drug-free male alcoholic patients matched in age. Following the collection of baseline blood samples, all subjects were given non-emetic doses of apomorphine. The first group (17 subjects) received seven s/c injections of apomorphine (0.01 mg/kg body weight; every second day). To 10 subjects of group 2, apomorphine was given everyday sublingually (from 0.1 mg to 0.7 mg) during one week. The difference between the duration and severity of the acute and protracted withdrawal symptoms in patients treated with apomorphine and those of the control group was noted. Apomorphine was especially effective in ameliorating anxiety, improving sleep and reducing physical and psychological dependence on alcohol. 67 percent of those who were treated with apomorphine remained sober within 12 months as opposed to 35 percent of the control group. One hour after the first injection of apomorphine the mean of serum prolactin decreased significantly (from 9.5 $\pm$ 3.6 ng/ml to 3.7 $\pm$ 2.8 ng/ml; $p < .05$). One hour after the first sublingual administration of 0.1 mg of apomorphine the mean of serum prolactin concentration also decreased though insignificantly (from 7.71 $\pm$ 2.14 to 6.68 $\pm$ 2.47 ng/ml). A comparison of the prolactin responses prior to the first and after the last administration of apomorphine did not reveal, however, any changes. These effects of apomorphine are interpreted in relation to its ability to stimulate central dopaminergic neurons. The gradual decrease in the prolactin response in the process of treatment suggests a decrease in sensitivity of DA-receptors either due to drug-induced desensitization or due to a normal recovery process.

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PREDICTORS OF ALCOHOLISM IN DEPRESSED MEN

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Summary:

We analyzed the prevalence of alcoholism in men classified as "antisocial" depressives, "anxious" depressives, and "pure" depressives. The antisocial depressives included all men with a diagnosis of antisocial personality (ASP). The "anxious" depressives included men who did not have ASP but had mainly "anxiety" disorders (panic, generalized anxiety, obsessive-compulsive, phobic, or "other" psychiatric disorder). The pure depressives included men with only major, minor, or intermittant depression.

The antisocial depressives had the highest rate of alcoholism; the "anxious" depressives, the next highest rate; and the pure depressives, the lowest. Both the antisocial and "anxious" depressives reported high levels of subjective anger.

Psychosocially, the antisocial and "anxious" depressives had more early childhood disruption, and genetically the antisocial depressives had a higher risk of alcoholism in their first degree relatives than the non antisocial depressives. When non affective psychopathology was present, it preceeded heavy drinking which in turn preceded the onset of the first major depressive episode.

We performed a stepwise logistic regression with alcoholism as the dependent variable. We entered subjective anger, diagnostic subclassification (antisocial, "anxious", pure), drug use disorder, age, family disruption, and a family history of alcoholism, antisocial personality, or drug use disorder as independent variables. Only drug use disorder, a family history of alcoholism in the male first degree relatives, and subjective anger were important in predicting alcoholism.

The most fascinating finding was the relationship of excessive anger to alcoholism. This is important because it identifies an emotional component of this behavioral disorder and is compatable with the suggestion that limbic system dysfunction may influence its pathogenesis.

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AMINO ACIDS, DEPRESSION AND AGGRESSION IN ALCOHOLICS

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Summary:

Our aim was to investigate whether serotonin metabolism is modified in alcoholics suffering from depression or exhibiting suicidal or aggressive tendencies. The indoleamine theory of affective disorders postulates that depression is associated with a functional serotonin deficiency. More recently it has also been suggested that a serotonin deficiency plays a role in other types of behavior: suicide and aggression. Brain serotonin has been shown to depend on the availability from the circulation of its precursor, tryptophan. It depends also on the plasma concentration of other amino acids which compete with tryptophan for brain entry: tyrosine, phenylalanine, valine, leucine, isoleucine and methionine. The ratio of tryptophan over these amino acids (tryptophan ratio) correlates with brain serotonin. We decided to assess whether alcoholic patients exhibiting depression, suicide or aggression have lower values for the tryptophan ratio. Presence of depression and prior episodes of depresion were assessed with the SADS. Patients judged to be depressed at the time of the study had all a past history of depression. None of the patients exhibited overt aggressive behavior at the time of the study but some had a past history of aggression. Incarceration for assaultive behavior against people or property was used as our criterion of past aggression history. A significant correlation was found in our patient population between aggression histories and depression. Tryptophan ratio values, determined after an overnight fast, were compared for the following groups of patients: group I (n=27), patients who never experienced depression and had no aggression history; group II (n=9), patients who were depressed but had no aggression history; group III (n=9), patients with both depression and an aggression history. Group III patients had the lowest tryptophan ratio value ($\bar{x} \pm SE = .064 \pm .008$). That value differed significantly from values observed for group I patients ($.117 \pm .005$) and for group II patients ($.105 \pm .006$). Two of the three patients who had attempted suicide fell into the group of patients with an aggression history. In conclusion, our data suggest the existence of an association between amino acid abnormalities, known to result in decreased brain serotonin, and manifestations of depression, suicide and aggression in alcoholics.

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PLATELET UPTAKE OF SEROTONIN IN CHRONIC ALCOHOLICS

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Summary:

Animal and human studies suggest that alcohol intoxication alters serotonergic metabolism. Blood platelet 5-HT uptake has been suggested as a model for neuronal serotonin metabolism. We wished to determine if platelet 5-HT uptake might be abnormal in chronic alcoholics. Because diminished 5-HT uptake has also been demonstrated in primary affective disorder and schizophrenia, we excluded patients with history or current diagnosis of either illness.

Subjects were male inpatients, ages 24-55, all of whom met DSM III criteria for alcohol dependence. Patients were approximately two weeks past admission and had been medication-free for $\bar{x}$ 8.6 days following detox with chlordiazepoxide. Controls were age-matched and free of any psychiatric or medical illness. All patients and controls completed a Beck Depression Inventory (BDI) and were administered a Hamilton Depression Scale (HDS) the day of drawing. The 5-HT uptake was determined as previously described by a modification of the method of Tuomisto and Tukianien.

The platelet 5-HT uptake of alcoholics was significantly lower than controls ($p < .008$). (The mean of the control group was similar to that reported in a previous study of nonalcoholics.) The 5-HT uptake did not correlate with time since admission, dose of chlordiazepoxide administered, severity of withdrawal, or time since last medication. While patients had significantly more symptoms of depression than did controls, the mean of both groups was well below the minimum criteria for depression. Three patients scored greater than 21 on the BDS but no patients scored greater than nine on HDS. There was no correlation between scores on BDI or HDS and 5-HT uptake. These findings support the hypothesis that reduced 5-HT uptake in these patients was not due to depression or prolonged and severe withdrawal.

Other studies suggest that altered CSF levels of serotonin metabolites in alcoholics reflect abnormal central serotonergic neuronal systems, which may contribute to the pathophysiology of alcoholism. We recently reported that alcohol intoxication produces a small but statistically significant increase in 5-HT uptake in nonalcoholic subjects. Because altered blood platelet 5-HT uptake may reflect altered neuronal 5-HT uptake, our findings of a decrease in platelet 5-HT uptake in alcoholics suggest that a dysfunction in neuronal transport of serotonin may exist in these patients. Indeed, alcohol consumption may serve to temporarily correct such a defect. This hypothesis is highly speculative and will require further testing.

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MEDICAL RISK SLOWS BRAIN RECOVERY IN ALCOHOLISM

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Summary:

Alcoholics commonly manifest impaired neuropsychological (NP) performance. It is generally thought that such deficits are caused by alcohol excess. We noted previously that even among those alcoholics who were screened to exclude obvious neuro-medical disease an increased prevalence of mild developmental, medical, and traumatic events was reported. In this study we examined the potential influence of such subclinical "premorbid risks" on NP outcome in alcoholics.

METHOD: We performed careful medical-developmental histories and NP examinations (Halstead Reitan Battery plus memory tests) on two groups of alcoholic men and matched nonalcoholic controls. Group 1 were alcoholics abstinent 4 weeks (N=71; age=41.5 $\pm$ 8.8; years alcoholic=13.8 $\pm$ 8.6), Group 2 were alcoholics abstinent 4 years (N=65; age=42.6 $\pm$ 8.4; years alcoholic=15.0 $\pm$ 7.4), and Group 3 were controls (N=68; age=42.2 $\pm$ 9.1). To explore the possible independent and joint contributions of duration of abstinence, aging, and premorbid risk on NP performance we conducted a 3X2X2 multivariate analysis of variance (MANOVA) with 3 groups, age split (<40 vs. ≥ 40), and presence vs. absence of positive risk history as independent factors and a selection of 14 NP tests and indices as dependent variables.

RESULTS: We found the expected age main effect (worse performance by older persons in all groups), a weak group effect (worse performance by recently detoxified alcoholics on a few tests), but more importantly, a group X risk interaction. Detailed inspection of test results showed significantly worse performance by recently abstinent alcoholics who had positive risk histories. Long-term abstinent alcoholics and controls showed no risk effect.

CONCLUSION: Alcoholics who are at the end of their first month of recovery from alcoholic drinking are more likely to manifest cerebral dysfunction if they previously experienced mild neuromedical or developmental insults. Since risk alone does not predict functioning in alcoholics, we suggest that such subclinical insults either facilitate emergence of cerebral dysfunction in active alcoholics, and/or slow NP recovery in the context of abstinence.

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BIOLOGICAL MARKERS OF DEPRESSION IN ALCOHOLICS

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Summary:

Recently there has been increased interest in using biological variables to confirm the diagnosis of endogenous depression. Because of the high frequency of depressive symptoms in alcoholic patients, we planned this study to determine if a subgroup or subgroups of alcoholics have biological test abnormalities similar to those found in affective illness patients. The biological variables we assessed are REM latency period, TSH response to thyrotropin releasing hormone (TRH), and the dexamethasone suppression test (DST). DSM III psychiatric diagnoses were made utilizing the NIMH Diagnostic Interview Schedule. To date we have studied 39 male patients hospitalized in a VA Alcoholism Treatment Unit. The patients had a mean age of 35.6 years (range 26-42), and a mean of 8.5 years of alcohol abuse (range 2-23). Patients with concurrent severe liver disease, endocrine abnormalities, and other major medical illness were excluded from the study. Testing was done following a 21-day detoxification period.

Of the 39 patients 8 (21%) had a diagnosis of current major depression, an additional 10 (26%) had a lifetime diagnosis of depression, and 21 (54%) had no depression. Of 33 patients for whom EEGs were obtained 16 (49%) had abnormal REM latencies (<60 min.); 9 of 39 patients had TRH test blunting (ΔTSH <7 mIU); and 2 of 39 had abnormal DST results (8 A.M. or 4 P.M. serum cortisol >5 mcg/dl). Among current depressed patients 2 of 7 (29%) had an abnormal REM latency, 3 of 8 (38%) an abnormal TRH, and 1 (13%) an abnormal DST. Among patients with a history of depression 5 of 6 (83%) had an abnormal REM latency, 3 of 10 (30%) an abnormal TRH, and none an abnormal DST. Among non-depressed patients 9 of 18 (50%) had an abnormal REM latency, 3 of 21 (15%) an abnormal TRH, and 1 of 21 (5%) an abnormal DST. Approximately 50% of the patients in each diagnostic group had one or more biological variable abnormality; correlation between TRH and REM latency results was not noted.

Our results indicate that the DST is not useful in this patient group, since negative results do not have diagnostic value. Shortened REM latency, found in all diagnostic groups, seems to lack specificity as a depression marker. The higher percent of TRH abnormalities in the depressed groups suggests that the TRH may ultimately prove to be of value for confirming the diagnosis of depression in alcoholics.

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PSYCHOPATHOLOGY AND ALCOHOLISM IN WOMEN ALCOHOLICS

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Summary:

This investigation explores the significance of psychiatric diagnosis as a differentiating variable for subgroups of women alcoholics. Fifty consecutive admissions to an alcoholism outpatient clinic were systematically interviewed and classified into 3 subgroups according to DSM III criteria: women alcoholics with a) no additional diagnosis (NAD), b) concurrent affective disorder (AD), and c) concurrent personality disorder (PD). The Addiction Severity Index (ASI) and the Beck Depression Inventory (BDI) were also administered. Depression and sobriety were reassessed at 3 month intervals. The 3 subgroups were examined for differences in socio-demographic and background characteristics, alcoholism and psychiatric history, presenting problems and beginning course of treatment.

The 3 subgroups did not differ on demographic characteristics or alcoholism history. This predominantly middle aged, white, unmarried, unemployed but well educated sample of women alcoholics evidenced similar histories in onset and course of alcoholism. However, at intake both psychiatric subgroups revealed significantly greater impairment than the NAD subgroup on 5 of the 7 domains assessed by the ASI. Thus, concurrent alcoholism and psychopathology interacted to produce a more impaired alcoholic with greater needs for vocational, family and psychological intervention as well as alcoholism and drug counseling. While periods of depression with suicidal ideation characterized the total population, AD alcoholics reported more frequent suicide attempts and significantly more depressive symptomatology (BDI) at intake and 3 months of treatment than did NAD alcoholics. PD alcoholics maintained an intermediate position. Preliminary finding indicate that despite greater initial impairment and ongoing depression at 3 months of treatment, AD women alcoholics established more stable sobriety (fewer slips) than either NAD or PD alcoholics. The implications of differentiating subgroups of women alcoholics will be discussed with reference to patient/treatment match.

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DEPRESSION MEASUREMENT IN ALCOHOLICS

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Summary:

There is widespread agreement that depression is an important factor in alcoholism. However, specific rates reported vary widely, from 9-98%. One potential source for such variation is the particular way depression is measured. This study compared 5 widely-used measures of depression: DSM-III (by checklist), Hamilton Depression Scale (HAM-D), Beck Depression Inventory (BDI), MMPI-D Scale (MMPI-D), and the 1 mg. Dexamethasone Suppression Test (DST). All measures were obtained on 51 consecutive males on admission to an Alcoholism Treatment Program. In addition, past history (PHx) and family history (FHx) of affective disorders and alcoholism were obtained.

Percentage of alcoholics classified depressed were: DSM-III (Dysthymia or Major Depression) -12%, DST (>5 μg/dl.) -21%, HAM-D (>15) - 16%, BDI (>13) - 36% and MMPI-D (>70) - 45%. Using DSM-III as the criterion variable, HAM-D showed good agreement, with 100% specificity, 96% sensitivity, and a κ = 0.84. None of the other methods showed good agreement, with DST showing low sensitivity, (33%) and fair specificity (80%), MMPI-D showing the opposite (sens. = 83%, spec. = 60%), and BDI intermediate (sens. = 67%, spec. = 69%). κ coefficients ranged from 0.16 to 0.29. Interestingly, these other measures were not highly intercorrelated; even the MMPI-D and BDI, both self-reports, correlated only moderately (r = 0.45). As expected, PHx and FHx of depression were weakly correlated with DSM-III and HAM-D, but not with DST, MMPI-D or BDI.

Rates of depression in alcoholics thus vary significantly depending on the way it is measured. Syndromal depression (DSM-III) occurs least frequently, while self-report measures, (MMPI-D, BDI) show high depression more frequently. The Hamilton Depression Scale appears to be a good alternative to DSM-III in that it apparently measures a very similar depressive entity. Further implications and possible explanations for the results will be discussed.

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THYROTROPIN-RELEASING HORMONE TESTING OF COCAINE ABUSERS

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Summary:

Clinical manifestations of cocaine intoxication, such as increased energy, hyperactivity, diaphoresis, hyperthermia and cardiovascular arousal, are remarkably similar to symptoms of hyperthyroidism. Conversely, the abrupt cessation of cocaine abuse often results in symptoms resembling hypothyroidism, such as fatigue, depression, psychomotor retardation, and hypersomnia. Since cocaine has profound noradrenergic (NE) effects, and NE is involved in thyrotropin-releasing hormone (TRH) regulation, it is plausible that thyroid axis disruptions contribute to the neurovegetative changes found in cocaine abuse. We studied 17 consecutive patients admitted with cocaine abuse by DSM III criteria, and with confirmatory plasma or urinary titers. Patients were excluded if they met DSM III criteria for other substance abuse or for major affective disorders. Twenty normal controls, similar in age and sex, and without substance abuse or major affective illness, were also studied. Each subject received a TRH test with cocaine patients tested during their first week of hospitalization. The TSH response to TRH (500 ug IV) was calculated as peak minus baseline TSH (ΔTSH). There were no significant differences in baseline T3, T4 or TSH levels between the two groups. However, the Δ TSH scores of cocaine patients (7.4 $\pm$ 3.3 uIU/ml) were significantly lower ($p < 0.001$, df=35, t=4.59) when compared to the controls (13.4 $\pm$ 4.2 uIU/ml). In addition, 8 of 17 cocaine patients (47%) had a blunted TSH (<7 uIU/ml) compared to none of the controls (Chi Square (1)=9.27, $p < 0.01$. Our data demonstrate inadequate TSH responses to TRH in cocaine abusers. This finding is consistent with our present knowledge regarding TRH regulation by biogenic amines. Direct hypothalamic administration of norepinephrine results in TRH release. Chronic cocaine abuse could lead to chronically elevated TRH, down regulation of the receptors for TRH in the anterior pituitary and subsequent blunting of the TSH response to TRH. Cocaine intoxication could produce a state of compensated hyperthyroidism which is only evident on TRH testing. While cocaine intoxication could produce thyroid axis activation by releasing TRH, the sudden cessation of cocaine use might result in thyroid axis inhibition due to the presence of desensitized thyrotroph TRH receptors. Thyroid axis inhibition at the level of the pituitary thyrotroph was found in our cocaine patients, and could partially explain the neurovegetative symptoms associated with the cessation of cocaine abuse. Reversal of cocaine abstinence symptoms may depend upon normalization of the thyroid axis and NE neuronal systems.

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ATTACHMENT ASSESSED IN HOSPITALIZED ADOLESCENTS

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Summary:

Twenty-two follow-up studies (Gossett, 1983) of inpatient treatment of severley disturbed adolescents show average improvement in 75% of personality disorders and 35% of psychotic disorders. Few quantitative studies exist of specific treatment processes such as the containment process and the development of inpulse control or the development of realistic self-esteem through modifying the patient's helplessness or grandiosity. Our study investigates symbiotic attachment by adolescents to staff or others and the subsequent individuation process as a part of hospital treatment. Changes in attachment are then observed in relation to changes in the disorder.

We report a new Quality of Attachment Assessment (QA) based on a standardized, tape-recorded, semi-structured, research interview. Five Summers Scales and five PTR Scales are applied which evaluate such dimensions of attachment as possessiveness, separation anxiety emotional dependency and instrumental dependency. Interrater reliability is significant ($p<.001$). Research interviews with patients generate data which agree with data from concurrent staff interviews about the patient, ($r=.50$, $p<.001$).

To date, 270 assessments have been made on 70 patients aged 10-18 years. Data is at three points in treatment: after admission, one year later and at discharge. Data on severity of illness is independently obtained using the Global Assessment Scale (Spitzer & Endicott, 1976). Ratings of clinical improvement are obtained using Clinical Global Improvement Scale. (Interrater reliabilities: GAS=92%; CGI=96%).

Clinical observations indicate that early in their hospitalization, severely disturbed adolescents tend to form intensely dependent relationships which then neutralize as the disorder improves and as a separation-individuation process proceeds. We hypothesized, therefore, that while adolescents are undergoing long-term, psychoanalytically-oriented hospital treatment, they would show a positive correlation between severity of illness and intensity of attachment. The second hypothesis was that intensity of attachment would be negatively correlated with clinical improvement.

Both hypotheses were confirmed by rejecting the null hypothesis. Depending upon the correlation, significances ranged from $p<.05$ to $p<.005$, after statistically partialling out the correlations between attachment and age and attachment and duration of hospitalization.

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ECT: CLINICAL VARIABLES AND OUTCOME

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Summary:

Although electroconvulsive therapy (ECT) is effective in certain psychiatric disorders, variables associated with outcome warrant investigation. To evaluate clinical variables, 66 patients who received ECT were studied consecutively. The decision to use ECT, laterality of administration, and number of treatments were determined by an attending psychiatrist independent of the study. ECT was administered three times weekly using brief pulse stimulation and EEG monitoring; 95% of subjects received bilateral treatments. Fifteen of the subjects were studied prospectively using the Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI), Mini-Mental Status Examination, and Mania Rating Scale. For retrospective analysis, hospital charts were reviewed and two investigators blindly assessed outcome using a four point scale. DSM III diagnoses were assigned to all patients; 91% received an affective disorder diagnosis.

In the prospective study, final outcome was correlated with response at the fourth treatment ($r_s = 0.603$, $p < 0.05$). Based on the HDRS, three patterns of response were seen at the fourth treatment: 1) complete (HDRS $\leq$ 6), 2) partial, and 3) negative. With subsequent treatments, 7 of 8 early complete responders remained well, while two of four early partial responders and none of the early negative responders became complete responders.

Eighty percent of the subjects studied retrospectively had a favorable outcome, defined as a partial or complete remission of symptoms. Diagnosis was related to outcome; 93% of subjects with affective disorders in the absence of preexisting nonaffective psychiatric illness improved. Total seizure time was correlated with outcome ($r_s = 0.426$, $p < 0.01$, $N = 62$); 88% of patients who obtained more than 300 seconds responded favorably ($\chi^2 = 6.80$, $p < 0.01$). Age and mean seizure length also correlated with outcome. Peripheral seizure time, number of treatments, use of psychotropic medications during ECT, and sex were not associated with outcome.

In conclusion, accurate diagnosis, early response pattern, and EEG seizure time may be helpful in predicting outcome and optimal length of ECT course in individual patients.

NR182 Thursday, May 10, 12 Noon-2:00 P.M.

CO-PATIENT RELATIONSHIPS ON AN INPATIENT UNIT

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Summary:

Patients on inpatient psychiatric units often become emotionally and/or sexually involved with each other. The incidence and nature of those involvements, however, is unknown leading to therapeutic interventions that are speculative. A prospective study was carried out over a two-year period at a private non-profit university-affiliated psychiatric hospital with an average length of stay of 16 days. Nursing staff on all shifts on a 24-bed general unit completed the patient relationship survey (PRS), designed to gather information on event/involvement and patients' characteristics, whenever they observed two patients becoming either emotionally and/or sexually involved with each other in ways different from what is usual on inpatient units. Data was analyzed using Chi-square and two-tailed t-tests.

Sixty-four PRS forms involving 102 patients were completed during the two years of the study. 1) The incidence of these involvements was 10.7%. 2) Patients who became involved with each other were younger than the rest of the patient population and were more likely to have a diagnosis of eating disorder, personality disorder or bipolar disorder. 3) Seventy-five percent of the involvements were reciprocal between the patients. In non-reciprocal involvements, men were more often the initiators, were seen as impulsive and seductive, and had multiple diagnoses including personality disorders and substances abuse, while the women partners were seen as sad and withdrawn, and had diagnoses of eating disorders and schizophrenia. 4) Married and unmarried patients do not tend to get involved with each other. 5) Most involvements were of an emotional and nonsexual nature. 6) Dependent patients were more likely to become involved with angry patients, and passive patients with impulsive patients. 7) There was a small core of patients with personality disorders, substance abuse and eating disorders who became involved repeatedly over time. 8) Most involvements were seen as healthy and appropriate by the nursing staff. 9) Most involvements occurred during times when the unit was calm. 10) There was no clear relationship between the leadership style and attitude to sexuality by the treating psychiatrists and their patients' involvements.

These findings suggest that copatient involvements on a short-term psychiatric unit are not a major problem, and what problems do arise can be anticipated in a small defined patient population.

NR183 Thursday, May 10, 12 Noon-2:00 P.M.

PARTIAL VERSUS INPATIENT SETTINGS: ONE AND TWO YEAR OUTCOMES

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Summary:

The study aim was to compare the relative cost effectiveness of behaviorally oriented treatment of alcohol abusers in a partial hospital and 24 hour inpatient setting. Previous studies comparing day hospital with extended inpatient treatment for psychiatric patients demonstrate that the partial hospital is as effective as inpatient treatment for a broad spectrum of patients, and clearly more cost effective. We hypothesized that this would be so for alcohol abusers as well. After 7 days of inpatient detoxification alcoholics were randomly assigned to treatment in the problem drinkers program, either as part of extended rehabilitation inpatient treatment or as a total treatment day care program. Average length of stay was three weeks. Patients were measured for drinking behavior and health in physical, psychological, social and life task areas. Patients were followed for two years and interviewed by phone on a monthly basis to reassess functioning. Records of arrests, deaths and rehospitalization costs were collected and significant others were also interviewed, bimonthly, to assess patient functioning.

Results: Overall, patients did equally well in both programs. However, day hospital treatment costs were one third less and remained significantly less throughout the two year follow-up. For patients in both treatment programs, drinking improved, and remained consistently low for the two years. Twenty percent of patients were rehospitalized during the first 6 months, 16%, 6 months to one year, and 11% in year two. For 18 months of follow-up, employment was significantly less than before treatment; however, by two years it had returned to pre-treatment levels. Social role functioning was significantly better after treatment than before and in year 2 was better than in year 1. Subjective well-being was improved at six months after treatment, and remained consistently high thereafter. Partial hospital patients had better well-being at six months than did extended inpatients but subsequently not significantly so. Patients continuously abstinent throughout the two years functioned no better than moderate drinkers; both had significantly better 2 year psychological, physical, and social health than did uncontrolled drinkers. While drinking was largely unrelated to other health areas one year after treatment, by two years it was closely associated with poorer functioning in these other health areas.