Multidimensional Hormonal Discrimination of Paranoid Schizophrenic From Bipolar Manic Patients

John W. Mason, Thomas R. Kosten, and Earl L. Giller

The search for biological markers of psychiatric disorders has traditionally involved univariate approaches, usually focusing upon one measure at a time, and to date has been primarily directed towards the assessment of depressive rather than psychotic illnesses. The present study explores a multidimensional psychoendocrine strategy, using a profile of five hormones, including cortisol, epinephrine, norepinephrine, testosterone, and free thyroxine, and is directed at the differentiation of two major psychotic illnesses, bipolar manic disorder and paranoid schizophrenia. When the levels of these hormones were assessed at admission and biweekly during hospitalization, the mean values for all five hormones were found to differ markedly between the two diagnostic groups. There was, however, always a zone of overlap in levels between the two groups when each of the five hormones were viewed individually, so that at best only about 70% of patients were correctly separated by diagnostic group using any single hormone alone. By contrast, multivariate approaches combining mean values of three or more hormones, using either stepwise discriminant analysis or multidimensional scaling, yielded 95% correct classification of the two diagnostic groups. Similar but not quite as great accuracy of classification was achieved with only the initial hormone sample obtained at the time of hospital admission. These preliminary findings provide encouragement for further exploration of multidimensional hormonal strategies in the search for useful biological criteria to assist in the diagnosis of psychiatric disorders.

Introduction

The search for laboratory tests to assist in psychiatric diagnosis and prediction of treatment response in recent years has focused largely upon depressive syndromes. Although this approach has yielded some promising results, it is increasingly clear that the clinical utility of such biological measures is still quite limited, particularly because of the relatively modest sensitivity, which ranges, for example, from only about 40%–70% with the dexamethasone suppression test (APA Task Force on Laboratory Tests in Psychiatry 1987). As a possible way of improving the sensitivity and clinical utility of such tests, we have in the present study explored a conceptual approach that differs in two basic presuppositions from the traditional model: (1) reliance upon a multivariate view of a profile of hormones rather than a univariate perspective that views a single hormonal

From the Department of Psychiatry, Yale University School of Medicine (JWM, TRK), New Haven, CT 06250, Medical Center/116A (JWM), West Haven, CT 06516, and the University of Connecticut Health Center, Farmington, CT 06032 (ELG).

Address reprint requests to John W. Mason, M.D., VA Medical Center/116A, West Haven, CT 06516.

Received January 30, 1990; revised August 13, 1990.

0006-3223/91/$03.50

measure in isolation; and (2) reliance upon the criterion of statistical differences in hormone levels between diagnostic subgroups rather than the supposition that a hormonal measure must show abnormal or pathological values (outside the "normal range," as used in defining glandular disease) in order to have clinical significance in relation to psychiatric disorders. These conceptual guidelines have emerged from basic research in the fields of stress and psychosomatic medicine (Mason 1968, 1974), but have not yet been examined for possible clinical application in general psychiatry.

In order to test the possible clinical utility of this conceptual approach we have focused on the differential diagnosis of paranoid schizophrenia versus bipolar manic disorder, since similarities in the symptom patterns for these two disorders can sometimes present significant difficulties in diagnosis (Pope and Lipinski 1978; Keisling 1981; Abrams and Taylor 1981; Carlson and Goodwin 1973; Ibe and Barton 1980). Patients with classic bipolar disorder can, in the manic phase, develop paranoid and Schneiderian "first-rank" symptoms usually associated with a diagnosis of schizophrenia. On the other hand, some schizophrenic patients may at times manifest hyperactivity, irritability, and grandiosity, which are usually associated with the manic phase of bipolar disorder. Lack of information at the time of hospital admission concerning the past longitudinal course of the illness can increase the difficulty of diagnostic and treatment decisions in these ambiguous clinical presentations. The importance of correct early diagnosis relates to several practical factors, including the effectiveness of lithium in both acute and prophylactic treatment of bipolar manic disorder, the quality of remission it induces, its greater patient acceptability, its lower cost, and its apparent lower risk of serious and irreversible side effects, coupled with increasing concern over the association of neuroleptic drugs with tardive dyskinesia and the pessimism widely connected with the label "schizophrenia." Some recent studies indicate that an admixture of manic and schizophrenic symptoms in the same patient is probably considerably more common than previously recognized and that overreliance on presenting psychotic symptoms has led to widespread overdiagnosis of schizophrenia and underdiagnosis of bipolar disorder, with consequent underutilization of lithium treatment for mania (Pope and Lipinski 1978; Keisling 1981; Abrams and Taylor 1981).

In this context, the development of useful biological criteria to aid in the differential diagnosis between schizophrenia and bipolar manic disorder would be a valuable contribution. As yet, there has been very little reported effort to apply neuroendocrine approaches to this specific problem. One study revealed that the thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone (TRH) infusion is less in manic than in undifferentiated schizophrenic patients, but the TSH values showed considerable overlap between the two patient groups, so that this test alone appears to have little, if any, practical value in this differential diagnosis (Extein et al 1980, 1982). We have recently reported that urinary free cortisol levels are significantly lower in paranoid schizophrenic than in bipolar manic inpatients (Mason et al 1986), as are urinary norepinephrine and epinephrine (Kosten et al 1987) and serum free thyroxine levels (Mason et al 1989), whereas serum testosterone levels are significantly higher in paranoid schizophrenic than in bipolar manic patients (Mason et al 1988a). However, none of these hormonal measures alone was sufficiently sensitive to provide the classification accuracy needed to completely separate the two diagnostic groups. The purpose of the present article, therefore, is to reexamine the above body of data as a whole and to explore the possibility that an integrative multivariate approach, using statistical analyses that combine the discriminating power of the above five hormones as a pattern or profile, might yield significantly greater classification accuracy than any single hormone can alone.

Patients and Methods

Ten paranoid schizophrenic (PS) and ten bipolar I, manic (BP) male inpatients were studied at the West Haven VA Medical Center. Diagnoses were based upon Research Diagnostic Criteria (RDC) criteria (Spitzer et al 1978) following the Schedule for Affective Disorders and Schizophrenia (SADS) interview (Endicott and Spitzer 1978). Diagnostic assessment was reviewed during the course of hospitalization and no within-admission changes in diagnosis were found in these patients. Written informed consent was obtained after full explanation of our purpose and procedures. None of the patients was experiencing his first episode of psychiatric illness, and those with recent substance abuse, major medical illness, or organic brain syndromes were excluded. The two diagnostic groups were demographically similar, and there were no significant differences in age (PS = 33.5 ± 4.2, BP = 40.7 ± 3.1, $t = 1.37$, $p < 0.2$), weight, or height between the groups. At the time of hospital admission, eight PS patients and nine BP patients were receiving antipsychotic medication, three BP patients were receiving lithium, and none of the 20 patients was receiving antidepressants. At the time of hospital discharge, five BP patients and one PS patient were receiving lithium, one PS patient was receiving an antidepressant, and ten PS patients and six BP patients were receiving antipsychotic medication. A detailed evaluation presented in the results section indicates that such factors as medications, severity of illness, or hospital stay did not play a significant role in our findings.

Following hospital admission and at 2-week intervals thereafter, 24-hr urine samples were collected at −20°C in a small freezer on the ward in order to preserve both the cortisol and catecholamine contents, and 9 AM serum samples were obtained for testosterone and free thyroxine measurements. Brief Psychiatric Rating Scale (BPRS) assessment of symptoms was obtained on the same day that hormone samples were collected. The number of samples averaged four per patient. No sampling was done on days of unusual physical activity, such as ward outings, nor in periods when any unusual clinical procedures were being performed. Completeness of urine collections was monitored by staff workers and urinary creatinine excretion was used as a check against grossly incomplete collection. Mean creatinine excretion was 1.6 g/day in the PS group and 1.7 g/day in the BP group (normal range 0.8–2.0 g/day). Although some day-to-day fluctuation in creatinine excretion does occur in relation to stress or other factors, it provides some help in detecting major losses of urine during the collection period. After processing, including adjustment of the urine catecholamine aliquot to pH 2.0 together with addition of EGTA/reduced glutathione solution, all urine and serum samples were stored at −70°C until analysis. Radioimmunoassay determinations were made of urinary free cortisol, using an extraction procedure (Clinical Assays, Inc., Cambridge, MA), of serum testosterone (Serono Laboratories, Braintree, MA), and of serum free thyroxine (Clinical Assays, Cambridge, MA) levels, while radioenzymatic determinations were made of urinary norepinephrine and epinephrine (Upjohn, Kalamazoo, MI) levels, all by commercially available kits as described and evaluated previously (Mason et al 1986, 1988a, 1989; Kosten et al 1987). The interassay coefficients of variation were 10.7% for the catecholamines, 4.0% for cortisol, 6.0% for testosterone, and 4.2% for free thyroxine.

Data analysis for comparisons involving single hormones used *t*-tests, since the values had a relatively normal distribution. When combining values for several hormones, we used two procedures that represent quite different and independent statistical strategies, stepwise discriminant analysis (SDA) and multidimensional scaling (MDS). SDA (BMDP

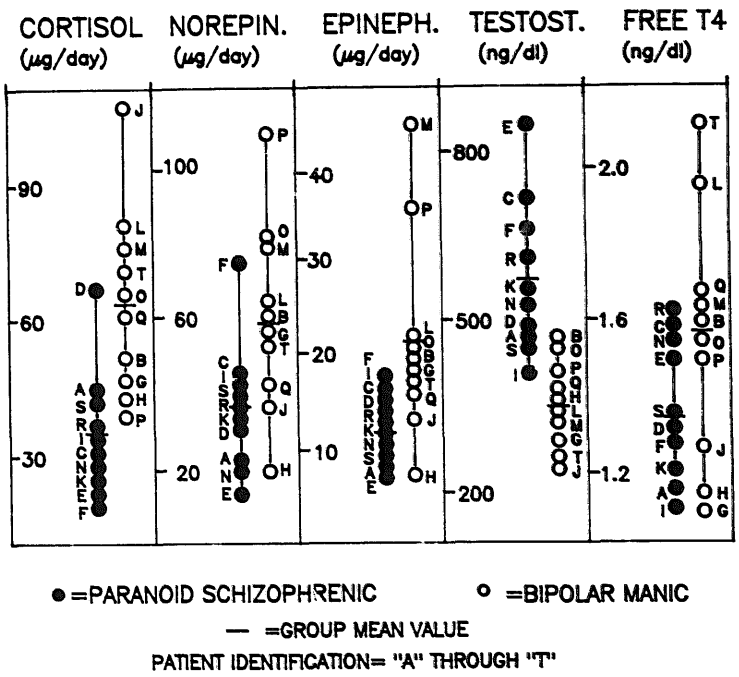

Figure 1. Univariate comparison of paranoid schizophrenic and bipolar manic patients using mean values of five hormones separately.

Statistical Software, Los Angeles, CA) is based on linear regression techniques and uses continuous variables such as hormone levels as independent variables with nominal dependent variables such as diagnosis (Draper and Smith 1966). MDS (Systat, Evanston, IL) is based on clustering algorithms and uses associations among the different hormones for each individual patient in order to determine which patients are most similar in overall hormonal profile (Takani et al 1976; Kruskal and Wish 1978; Gattaz et al 1985). Euclidean distances between points (patients) are then computed and can be plotted in multidimensional space. For our purposes, a two-dimensional plot is used.

Results

Figure 1 presents the mean hormone values for the total hospitalization period on all individual patients and reveals the differences between the PS and BP group means for all five hormones as follows: cortisol, 36 versus 62 μg/day ($p < 0.003$), norepinephrine, 36 versus 60 μg/day ($p < 0.03$), epinephrine, 13 versus 21 μg/day ($p < 0.03$), testosterone, 559 versus 343 ng/dl ($p < 0.0006$), and free thyroxine, 1.35 versus 1.54 ng/dl ($p < 0.1$). The filled circles represent individual schizophrenic patients and the open circles symbolize the bipolar patients. Individual patients are identified in all the graphs by the letters from "A" to "T" alongside the symbols. An analysis focusing only on the first hormone sample following hospital admission yielded a similar pattern of differences between the PS and BP group means as follows: cortisol, 43 versus 75 μg/day ($p < 0.05$); norepinephrine, 46 versus 78 μg/day ($p < 0.06$); epinephrine, 16 versus 26 μg/day ($p < 0.1$); testosterone, 546 versus 374 ng/dl ($p < 0.03$); and free thyroxine, 1.39 versus 1.68 ng/dl ($p < 0.03$). For both the mean values (Figure 1) and the admission values, however, there was always overlap between the lowest individuals in the higher group

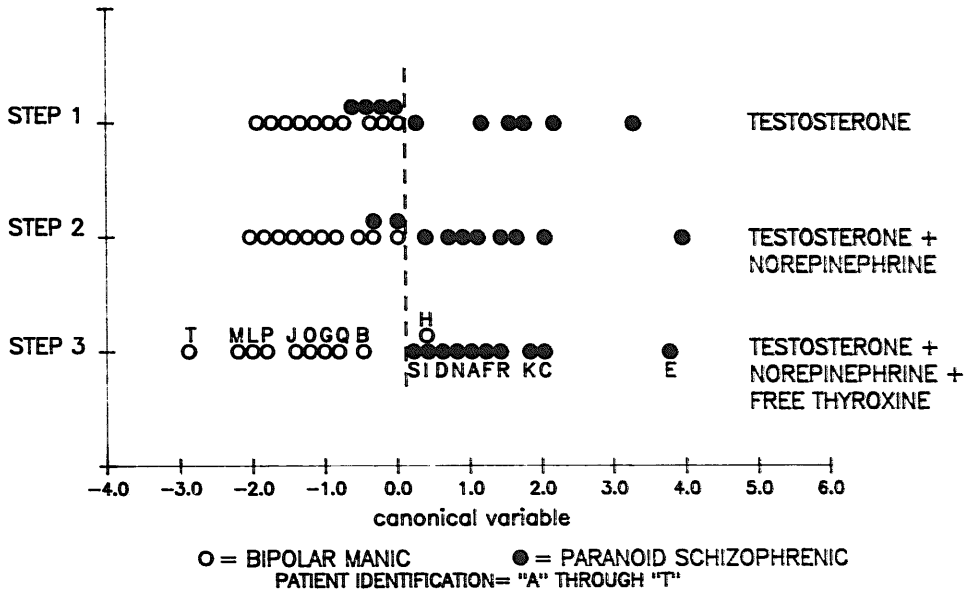

Figure 2. Multihormonal differentiation of paranoid schizophrenic and bipolar manic patients with stepwise discriminant analysis using mean levels of three hormones (testosterone, norepinephrine, free thyroxine)

and the highest individuals in the lower group, with at least six patients from the two groups in a common zone, so that no single hormone alone can provide the necessary discriminating power for a clinically useful biological criterion for this differential diagnosis. The next step, then, is to explore the utility of multivariate approaches that can combine the discriminating power of several hormones. For this purpose we turned to SDA and MDS because they represent two independent methods based upon different computational procedures with nonoverlapping statistical limitations (e.g., distributional and modeling assumptions) in their use.

SDA, using the mean hormonal values, is shown in Figure 2, with the final canonical equation for each step represented graphically on a single horizontal axis. The values for individual patients are indicated by filled circles for the schizophrenic and open circles for the bipolar patients. In stepwise fashion the graph depicts (1) the discriminating power of testosterone alone, which fails to separate four PS patients from the BP patients, (2) with the addition of norepinephrine, only two PS patients are misclassified, and (3) with the further addition of free thyroxine, all the PS patients are correctly classified and only one BP patient is misclassified, the two diagnostic groups now being separated with 95% classification accuracy by this discriminant function. Using the mean values for these hormones, the constant was 0.0077, and the coefficients for the canonical variables were 0.0080 for testosterone, −0.0236 for norepinephrine, and −1.721 for free thyroxine. The mean value of the canonical equation for the schizophrenics was 1.31 and for the bipolar group was −1.31. A similar analysis was made with the initial admission hormonal values, and the resulting canonical equation provided 80% separation between patients in the two diagnostic groups, using only the single first sample in each patient. When three BP patients on lithium medication at the time of the first sample were eliminated, the classification accuracy increased to 94%.

Finally, the results of the MDS analysis are shown in Figure 3, using the mean values

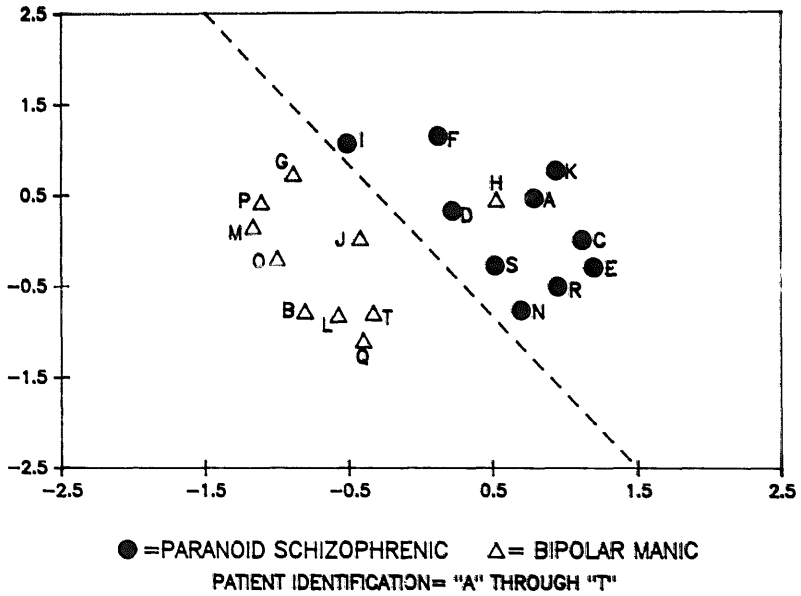

Figure 3. Multihormonal differentiation of paranoid schizophrenic and bipolar manic patients with multidimensional scaling using mean levels of five hormones (cortisol, norepinephrine, epinephrine, testosterone, free thyroxine).

for all five hormones: cortisol, norepinephrine, epinephrine, testosterone, and free thyroxine. The filled circles again represent the schizophrenics and the open triangles the bipolar patients. The dotted line passing through the intersection of the zero lines of the two axes in this two-dimensional plot separates all the schizophrenics on the right side versus all but one of the bipolar patients on the left side, the same patient misclassified by the SDA procedure, again yielding a classification accuracy of 95%. The stress factor values were 0.44, 0.22, 0.06, 0.004, and 0.007 for the five dimensions, respectively. The two-dimensional value of 0.22 does not quite reach below the 0.15 level usually recommended, as does the three-dimensional value of 0.06, but we have used the two-dimensional plot in this early stage to facilitate easy presentation on the printed page and quick comprehension of this multivariate model, even though the three-dimensional analysis provides still better discrimination of the two diagnostic groups. The orientation of the two axes and the labeling of the two dimensions represented in this plot are arbitrary, but based upon the distribution of the two "clouds" of patients, the horizontal axis appears to be the one mainly related to hormonal differences between these two diagnoses. An understanding of the significance of the vertical axis will require further study, probably best accomplished with a broader range of clinical measurements than simply the BPRS. A similar analysis was made with only the admission hormonal values on patients free of lithium medication and all bipolar patients were correctly separated to the left side of the plot, but in this case two schizophrenic patients were misclassified for an overall classification accuracy of 88%.

It is important to emphasize that this procedure does not use the diagnostic difference to search for hormonal differences, as does the SDA procedure, but that MDS simply plots patients together or apart depending upon the similarity of interrelationships among all five hormones, namely the similarity of the overall configuration of the hormonal profile among individuals. Thus, the distribution of patients in the plot is based entirely

upon biological criteria, and the diagnostic identifications were added subsequently to clarify the presentation of results.

We next examined whether the hormonal differences between the two diagnostic groups might be related to differences between the groups other than diagnosis. At the time of hospital admission, which is the period of greatest interest in terms of the possible diagnostic utility of our findings, eight PS patients and nine BP patients were receiving antipsychotic medication. The significance of this medication was evaluated in several different ways: (1) There was no significant difference between the two groups in the dosage (chlorpromazine equivalents) of antipsychotic medication (BP = 599 ± 169 mg versus PS = 570 ± 150 mg, $t = 0.130$, $p < 0.9$). (2) There were no significant correlations between antipsychotic medication dosage and the levels of any of the hormones used in our multivariate analyses. (3) As reported previously for each of the particular hormones used in this study, other analyses, including two-way analysis of variance (ANOVA) for diagnosis versus medication effects and comparison of large samples of patients receiving, versus those not receiving, antipsychotic medication, have not shown a significant role of medication in our findings (Mason et al 1986, 1988a, 1988b, 1989; Kosten et al 1987). However, future studies along this line will need to continue the evaluation of possible medication effects, especially with the study of larger numbers of medication-free patients and of hormonal levels during drug washout periods. It also will be of interest to evaluate such issues as the possibility that differential hormonal responses to neuroleptics might occur between diagnostic subgroups.

With regard to lithium, three BP patients were receiving this medication at the time of the first sample collection, and, as indicated earlier, their elimination from the analyses did not substantially change the findings, but tended, in fact, to improve classification accuracy with the multivariate procedures. It is also noteworthy that during the later course of hospitalization when more bipolar patients were receiving lithium medication, we observed that the bipolar patients still had higher free thyroxine levels than the schizophrenics (Figure 1), in spite of reports that lithium may lower thyroxine levels (Transbol et al 1978). None of the 20 patients was on antidepressants at the time of hospital admission and only one at the time of discharge.

Analysis of the duration of hospitalization revealed no significant difference between the two groups in the number of days of hospital stay (PS = 159.5 ± 29.3, BP = 102.3 ± 32.1, $t = 1.31$, $p < 0.2$). Finally, with regard to severity of illness as a possible confounding factor, we found no significant differences between the two groups in either the first (PS = 25.8 ± 3.8 versus BP = 25.9 + 4.9) or the mean (PS = 19.0 ± 2.9 versus BP = 16.8 ± 3.1) BPRS sum (total symptoms) scores.

Discussion

This study, then, pursues the observation that the levels of five hormones—cortisol, norepinephrine, epinephrine, testosterone, and free thyroxine—were significantly different in paranoid schizophrenic than bipolar manic male inpatients. Although mean values of no single hormone alone could separate more than about 70% of the patients correctly as schizophrenic versus manic, it was found that multivariate combinations of these hormones were able to classify correctly about 95% of the patients into these two diagnostic categories in our pilot sample. SDA correctly classified the diagnosis for all but 1 of 20 patients, using the mean values of only 3 hormones, testosterone, norepinephrine, and free thyroxine. However, this statistical procedure "knows" the correct diagnosis at the

outset and essentially conducts a search for the hormones and associated coefficients that will best discriminate the two diagnostic groups within that specific sample of patients, thereby setting up the possibility of a nongeneralizable separation if the original patient sample is atypical. Therefore, replication of results with SDA on a prospective basis with a second larger sample of patients is a very important future step with this procedure in order to establish predictive accuracy, particularly since this original patient sample is relatively small.

In view of this concern, we examined further the relationships among these hormones with a second descriptive multivariate procedure, MDS, which provided a two-dimensional plot from which 95% of the patients could be correctly classified, using the mean values of all five hormones for the total hospitalization period, with only slightly less accuracy using the single sample obtained at the time of hospital admission. The MDS analysis adds strength to the conclusion that there are different hormonal patterns in these two diagnostic subgroups, since this procedure does not "know" the diagnosis in its approach to subtyping, but rather the resulting classification is based solely upon biological criteria expressing the similarity in hormonal profile among patients. Based upon correlational analyses, patients with similar hormonal interrelationships are determined using a ranking of the distances between patients within five-dimensional space (one dimension for each hormone). This five-dimensional space is then reduced to a two-dimensional representation, while retaining as much as possible the distances between subjects (Kruskal and Wish 1978; Gattaz et al 1985). On these resulting two-dimensional plots in our study, we then identified the location of each patient and designated his clinical diagnosis. As illustrated in Figure 3, the discrimination thus provided between RDC-diagnosed paranoid schizophrenic and bipolar manic patients by the purely biological measurements used in this multivariate approach is remarkable.

Although the present findings can be viewed simply at a descriptive level and as providing supplemental biological criteria to broaden the present multiaxial descriptive clinical approach to psychiatric diagnosis, a compelling question is raised concerning the meaning of the hormonal differences between the two diagnostic subgroups, particularly with regard to the possible significance they may have for the pathogenesis or course of these illnesses. The historical and conceptual background for the present study has been building for a much longer period than is generally realized, with an early era of clinical psychoendocrine research in general psychiatry from about 1910 to 1950 (Reiss 1958; Mason and Docherty 1980), and a more recent period of basic psychoendocrine research within the field of stress and psychosomatic medicine (Mason 1968, 1974, 1975). A number of leads and guiding principles emerging from this earlier work appear to deserve careful consideration for their relevance to the objectives of modern biological psychiatry. Although measured at a peripheral level, hormones in a direct way represent central neuroendocrine effector output systems for final common pathway neurones in the hypothalamus, and, therefore, provide a window into central brain mechanisms viewed either at a psychological or neurochemical level. The current state of knowledge of relationships between specific neurotransmitter and specific neuroendocrine systems is still quite limited, so that it is probably too early to attempt to venture hypotheses concerning the possible meaning of our hormonal findings in terms of neuroregulator mechanisms. There is, however, a rather substantial body of knowledge concerning the linkages between hormonal and psychological mechanisms that can provide a framework for beginning to explore the clinical meaning of our findings. It is known, for example, that the relationship between hormonal and psychological mechanisms is bidirectional

and that hormonal levels can either reflect or influence psychological mechanisms. Such interactions can involve trait as well as state processes, including cognitive as well as emotional mechanisms, especially those relating to the organization of psychological defenses and coping styles (Mason 1975). The relatively low cortisol levels in paranoid schizophrenic patients, for example, may reflect the defensive effectiveness of a delusional system or of a denial mechanism in minimizing affective distress (Mason 1986). Similar hypotheses for the other individual hormones used in this study have been discussed previously (Kosten et al 1987; Mason et al 1988a, 1989) and appear to provide a reasonable beginning framework for pursuing the clinical implications of our findings from the standpoint of relationships between hormonal levels, psychological mechanisms, and clinical symptoms in these psychiatric disorders. It will also be of interest in future studies to compare the hormonal profiles of normal control subjects having minimal psychopathology with those of these subgroups of psychiatric patients.

Conclusion

Although we certainly emphasize the preliminary nature of the present pilot study and the need for confirmation in larger samples and in other populations, the concurrence of finding hormonal profiles yielding 95% classification accuracy with two quite different and independent multivariate methods does appear to provide encouragement for further exploration of this approach to the biological assessment of psychotic and affective disorders. More broadly, our findings place emphasis, along with related studies (Mason et al 1988b), on the usefulness of certain guiding principles for further work along these lines, including (1) the importance of working with relatively homogeneous psychiatric diagnostic subgroups, (2) the importance of longitudinal psychoendocrine assessment of patients during clinical recovery, (3) the importance of assessing the significance of differences in hormonal levels between groups of psychiatric patients within the medically defined "normal range," (4) the importance of not ignoring basal hormonal levels in searching for biological markers in psychiatry, and (5) the importance of multidimensional hormonal strategies as a promising approach to attaining considerably greater sensitivity and classification accuracy than has yet been possible with any single endocrinological measure alone.

Support for this work was provided in part by Veterans Administration research funds and National Institute of Mental Health research career award MH-00346 to J.W.M. and DA-00112 to T.R.K.

References

Abrams R, Taylor MA (1981): Importance of schizophrenic symptoms in the diagnosis of mania. *Am J Psychiatry* 138:658–661.

APA Task Force on Laboratory Tests in Psychiatry (1987): The Dexamethasone Suppression Test: An overview of its current status in psychiatry. *Am J Psychiatry* 144:1253–1262.

Carlson GA, Goodwin FK (1973): The stages of mania. *Arch Gen Psychiatry* 28:221–228.

Draper N, Smith H (1966): *Applied Regression Analysis*. New York: Wiley.

Endicott J, Spitzer RL (1978): A diagnostic interview: The Schedule for Affective Disorders and Schizophrenia. *Arch Gen Psychiatry* 35:837–844.

Extein I, Pottash A, Gold MS, Martin DM (1980): Differentiating mania from schizophrenia by the TRH test. *Am J Psychiatry* 137:981–982.

Extein I, Pottash A, Gold MS, Cowdry RW (1982): Using the protirelin test to distinguish mania from schizophrenia. *Arch Gen Psychiatry* 39:77–81.

Gattaz WF, Gasser T, Beckman H (1985): Multidimensional analysis of the concentrations of 17 substances in the CSF of schizophrenics and controls. *Biol Psychiatry* 20:360–366.

Ibe IO, Barton JL (1980): Schizophrenia to manic-depression. Mutation or misdiagnosis? *Am J Psychiatry* 137:742–743.

Keisling R (1981): Underdiagnosis of manic-depressive illness in a hospital unit. *Am J Psychiatry* 138:672–673.

Kosten TR, Mason JW, Giller EL, Ostroff RB, Harkness L (1987): Sustained urinary norepinephrine and epinephrine elevation in post-traumatic stress disorder. *Psychoneuroendocrinology* 12: 13–20.

Kruskal JB, Wish M (1978): *Multidimensional Scaling*. Beverly Hills, CA: Sage.

Mason JW (1968): Organization of psychoendocrine mechanisms. *Psychosom Med* 30:791–808.

Mason JW (1974): Specificity in the organization of neuroendocrine response profiles. In Seeman P, Brown G (eds), *Frontiers in Neurology and Neuroscience Research*. Toronto: University of Toronto Press, pp 68–80.

Mason JW (1975): Clinical psychophysiology: Psychoendocrine mechanisms. In Reiser M (ed), *American Handbook of Psychiatry*, vol 4, New York: Basic Books, pp 553–582.

Mason JW, Docherty JP (1980): Psychoendocrine research on schizophrenia: A need for reevaluation. In Baxter C, Melnechuk T (eds), *Perspectives in Schizophrenia Research*. New York: Raven, pp 131–144.

Mason JW, Giller EL, Kosten TR, Ostroff RB, Podd L (1986): Urinary free-cortisol levels in posttraumatic stress disorder patients. *J Nerv Ment Dis* 174:145–149.

Mason JW, Giller EL, Kosten TR (1988a): Serum testosterone differences between patients with schizophrenia versus affective disorder. *Biol Psychiatry* 23:357–366.

Mason JW, Giller EL, Kosten TR, Harkness L (1988b): Elevation of urinary norepinephrine/cortisol ratio in posttraumatic stress disorder. *J Nerv Ment Dis* 176:498–502.

Mason JW, Kennedy JL, Kosten TR, Giller EL (1989): Serum thyroxine differences between schizophrenic versus affective disorder diagnostic subgroups. *J Nerv Ment Dis* 177:351–358.

Pope HG, Lipinski JF (1978): Diagnosis in schizophrenia and manic-depressive illness. *Arch Gen Psychiatry* 35:811–828.

Reiss M (ed) (1958): *Psychoendocrinology*. New York, Grune & Stratton.

Spitzer RL, Endicott J, Robins E (1978): Research Diagnostic Criteria. *Arch Gen Psychiatry* 35: 773–782.

Takani Y, Young F, DeLeeuw J (1976): Non metric individual differences multidimensional scaling: An alternative least squares method with optimal scaling features. *Psychometrika* 42:7–67.

Transbol I, Christiansen C, Baastrop PC (1978): Endocrine effects of lithium. *Acta Endocrinol* 87:759–767.