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Disturbed Endocrine Function in the Psychoses

II: Discriminant Function Analysis of Multihormone Data

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Discriminant function analyses were performed on plasma concentrations of prolactin, growth hormone, cortisol, TSH, and the neurophysins measured over 17 hours in 70 newly admitted drug-free psychiatric patients and 35 control subjects. The hormone data distinguished between patients with different classes of drug-free psychosis (26 schizophrenic, 12 with manic disorder, 10 with major depressive disorder, psychotic subtype, 9 with schizoaffective mania (SAM)). Higher plasma cortisol and lower TSH concentrations separated eight of nine SAM patients from all others.

Theoretical relationships between the psychoses may be clarified by examination of the hormonal differences between psychoses. For example, one view of the psychoses is that they lie along a single continuum encompassing health, mania, depressive psychoses, schizoaffective psychoses, and schizophrenia. If biologically determined variables could satisfactorily distinguish between psychoses, and between psychoses and health, then the same variables may help determine the relative positions of each psychosis along a single continuum, and may identify boundaries between disorders (Kendell, 1975).

Few other studies have examined the utility of biological data in the classification of the major functional psychoses. From the limited information available, it is clear that schizophrenia can be distinguished from other, non-psychotic disorders and health using, for example, measures derived from the evoked potential (Shagass *et al*, 1985), but not from the affective psychoses. Similar studies have been reported using computerised axial tomography (Reider *et al*, 1983; Tsai *et al*, 1983), platelet serotonin concentrations (Stahl *et al*, 1983), positron emission tomography (Buchsbaum *et al*, 1984; Kling *et al*, 1986), and smooth-pursuit eye movement (Siever *et al*, 1984). These studies show that the biological basis of an inferred neural abnormality may not be specific for a single disorder, but can be found in most psychoses. Since many reported abnormalities are relatively enduring, they may be related to the biological susceptibility to psychoses, and may facilitate the separation of homogeneous groups for more detailed investigations (e.g. molecular genetic studies as suggested by Radouco-Thomas *et al*, 1984).

In the companion paper (Whalley *et al*, 1989 – this issue, pp. 455–461), we presented data pointing to differences in plasma hormone concentrations between diagnostic subgroups that could not be explained simply as endocrine responses to stress. We now report a discriminant function analysis of the same data. This approach avoids problems of statistical inference, but ideally requires replication with a new data set. Drug-free patients are difficult to locate and, especially when disturbed, difficult to study. We adopted the following solution. In the first stage of discriminant analysis, we included only control subjects and those drug-free psychotic patients in diagnostic groups large enough to be informative. In the second stage, we used the first two discriminant functions derived from the drug-free psychotic patients to classify the remainder of our sample. This comprised those patients who had received medication up to two weeks before blood sampling and who did not meet drug-free criteria, and those drug-free patients in diagnostic groups too small to be included in the discriminant analysis. The reasoning that lead to our use of discriminant analysis in this way is detailed by Kendell (1975, pp. 106–118).

Method

Ninety-eight patients routinely admitted to hospital and 35 control subjects were studied. They are fully described in the companion paper (Whalley *et al*, 1989), along with details of the diagnostic and investigative procedures.

Statistical analysis

The 35 control subjects and 57 drug-free psychotic patients in the four largest diagnostic groups (schizophrenia, $n = 26$; manic disorder, $n = 12$; major depressive disorder, psychotic subtype, $n = 10$; schizoaffective disorder, manic subtype, $n = 9$) were entered into a discriminant analysis: 41 patients were omitted, either because they had or may have received

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medication during the previous three months, or because they were in diagnostic groups too small for analysis. The latter group comprised: schizophrenia (6 patients), major depressive disorder, psychotic subtype (5), major depressive disorder, endogenous subtype (12), schizoaffective disorder, depressive subtype (3), minor depressive disorder (3), manic disorder (7, of whom 3 had a post-partum onset), and five patients with unclassified psychoses.

The prior probabilities of group membership were adjusted according to the distribution of cases among the largest diagnostic groups and control subjects. Variables were selected for inclusion in the discriminant analysis on the basis of the results of the ANOVA. Only those hormones with a between-group F ratio greater than 4.2 (d.f. 4, 87; $P<0.003$) were used.

Discriminant analysis derives a linear composite, the discriminant function, which maximally discriminates between groups. A discriminant score is provided for each subject that maximises the F ratio of the between-group and within-group mean squares in a univariate ANOVA.

Discriminant functions were derived by stepwise procedures using Wilk's method (Cooley & Lohnes, 1971). The stepwise selection criteria were determined by the overall multivariate F ratio for the test of differences between the centroids of each group. Scores on discriminant functions 1 and 2 were calculated for the remaining 41 patients not included in the analysis so far, and the resulting classification compared with their clinical grouping. The discrimination achieved between diagnostic groups by discriminant analysis was then compared with the results of two further discriminant analyses. In the second, 12 schizophrenic subjects were randomly removed and the analysis repeated. In the third, the control group was removed. These further analyses provided a test of 'spuriousness' of the results of the first analysis.

Results

Discriminant analyses

The first discriminant analysis (A) derived two functions that together accounted for 100% of the variance (functions 1A and 1B, Table I). Cortisol (p.m.) entered the analysis at $F=9.4$, TSH (ev.) at $F=8.8$, prolactin (p.m.) at $F=7.7$, and prolactin (a.m.) at $F=6.6$, and their standardised canonical discriminant function coefficients are given in Table I. Figure 1 shows plots of scores on functions 1A and 2A for the five diagnostic groups. Scores were then obtained for the 41 ungrouped subjects. Table II presents a classification of the 57 psychotic patients and 35 control subjects entered at this stage of the analysis and shows that eight of nine SAM patients were correctly identified, with no false positives. All 12 manic patients were correctly identified, with 35 (44%) false positives. When discriminant scores were obtained for the ungrouped cases, four (10%) were classified as SAM. These four comprised one schizophrenic, one major depressive disorder, psychotic subtype, and two unclassified psychoses.

The second (B) and third (C) discriminant analyses were undertaken to test the reliability of the first (A). After

TABLE I

Standardised discriminant function coefficients of transformed[1] plasma hormone concentration derived in three analyses (A, B, and C)

Hormone	*Time*	*Functions*[2]					
		1A	*2A*	*1B*	*2B*	*1C*	*2C*
Prolactin							
	a.m.	0.31	0.06	—	—	—	
	p.m.	0.00	0.95	0.30	0.68	—	—
	ev.	—	—	—	—	—	—
Cortisol							
	a.m.	—	—	—	—	0.67	0.74
	p.m.	−0.74	−0.16	—	—	—	—
	ev.	—	—	−0.78	−0.25	—	—
TSH							
	a.m.	—	—	—	—	—	—
	p.m.	—	—	—	—	—	—
	ev.	0.71	−0.18	0.69	−0.44	−0.87	0.18
Oestrogen-stimulated neurophysin							
	a.m.	—	—	—	—	—	—
	p.m.	—	—	—	—	0.59	−0.48
	ev.	—	—	−0.11	−0.68	—	—
% variance		73%	18%	68%	25%	96%	4%
Significance		$P<0.0001$	$P<0.004$	$P<0.0001$	$P<0.0001$	$P<0.0001$	$P<0.62$

1. See Table II of paper I (p. 458).
2. Functions 1A and 2A are obtained for 92 subjects (35 controls, 26 schizophrenics, 12 with manic disorder, 10 with major depressive disorder, psychotic subtype, 9 with SAM); functions 1B and 2B derived for the same subjects after randomly removing 12 schizophrenics; and 1C and 2C after removing control subjects.

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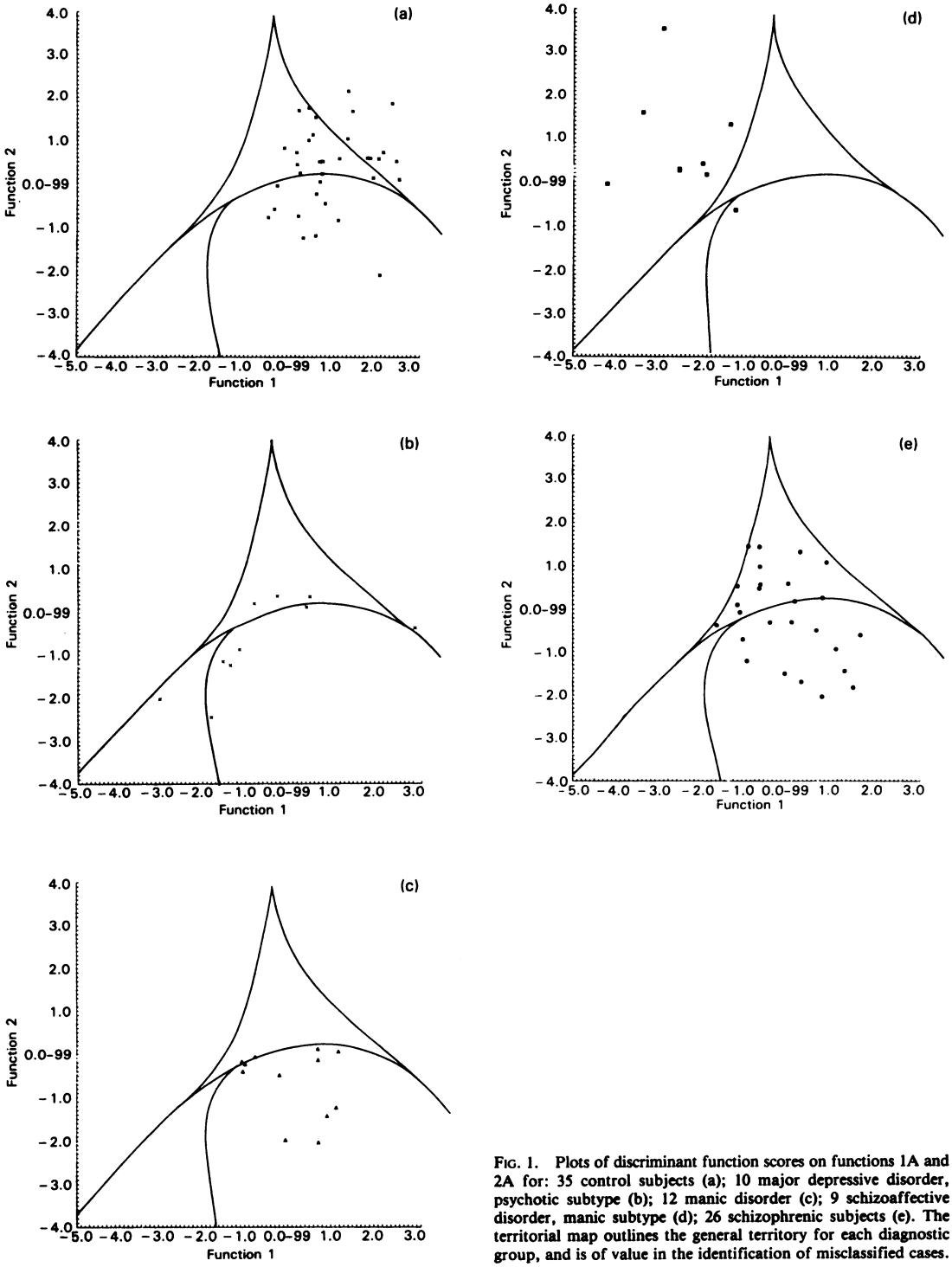


FIG. 1. Plots of discriminant function scores on functions 1A and 2A for: 35 control subjects (a); 10 major depressive disorder, psychotic subtype (b); 12 manic disorder (c); 9 schizoaffective disorder, manic subtype (d); 26 schizophrenic subjects (e). The territorial map outlines the general territory for each diagnostic group, and is of value in the identification of misclassified cases.

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TABLE II
Classification based on scores derived from functions 1A and 2A of the discriminant analysis

Actual group	n	*Predicted diagnostic group: no. (% correctly classified)*				
		Control	*Schizophrenia*	*Major depressive disorder, psychotic subtype*	*Schizoaffective disorder, manic subtype*	*Manic disorder*
Control	35	14 (40%)	8 (23%)	0 (0%)	0 (0%)	13 (37%)
Schizophrenia	26	1 (4%)	9 (35%)	0 (0%)	0 (0%)	16 (62%)
Major depressive disorder, psychotic subtype	10	1 (10%)	3 (30%)	1 (10%)	0 (0%)	5 (50%)
Schizoaffective disorder, manic subtype	9	0 (0%)	0 (0%)	0 (0%)	8 (89%)	1 (11%)
Manic disorder	12	0 (0%)	0 (0%)	0 (0%)	0 (0%)	12 (100%)
'Ungrouped' cases[1]						
Schizophrenia	7	0	2	0	1	4
Major depressive disorder, psychotic subtype	5	0	2	1	1	1
Major depressive disorder, endogenous subtype	9	0	1	0	0	8
Schizoaffective disorder, depressed subtype	3	0	1	0	0	2
Manic disorder	3	1	0	0	0	2
Manic disorder, puerperal onset	3	0	0	3	0	0
Unclassified psychoses	5	0	0	0	2	3

1. The ungrouped cases were not entered into the analysis.

randomly removing 12 schizophrenics, two functions were derived, accounting for 93% of the variance. Six of nine SAM patients were correctly classified, with one false positive (a control subject). The three misclassified SAM patients were grouped with major depressive disorder, psychotic subtype. The third (C) discriminant analysis did not include control subjects, and the two functions derived accounted for 100% of the variance. Six of nine of SAM patients were correctly classified by scores on these functions; all three misclassified patients were placed under manic disorder. There were no false positive SAM 'diagnoses'.

In summary, the discriminant analyses yielded functions based largely on the power of cortisol and TSH (ev.) concentrations to distinguish between SAM and other disorders, especially the affective psychoses. Classifications based upon these analyses yielded broadly similar results, remarkable by the consistency of the separation between SAM and other disorders, and the fact that so few other patients were misclassified by discriminant function scores as SAM.

Discussion

Discriminant scores based on higher plasma cortisol and lower TSH concentrations separated eight of nine SAM patients from all others and so provided further endocrine support for the distinction between SAM and other psychoses made by RDC (see Whalley *et al*, 1989).

Discriminant function analysis is a statistical method for testing a classificatory system with particular advantages over factor and cluster analyses (Moran, 1966; Kendell & Gourlay, 1970; Kendell, 1975). The validity of any distinction obtained between groups by discriminant analysis rests upon the analysis meeting four criteria. First, the covariance matrices for each of the diagnostic groups must be equal, otherwise spurious results may be derived (Kendell & Post, 1973). Second, the choice of items included in the analysis must be carefully evaluated and the number of subjects entered needs to be greater than the product of the number of items and the number of groups. These two criteria were met in the present study: there was symmetry of variance matrices, and the problem of item selection was solved by setting the F ratio for an item to enter the analysis at a conservatively high value. The third

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criterion for a valid distinction between diagnoses is that the two categories must have a bimodal distribution of scores on the discriminant function with a 'point of rarity' between categories. There was a clear visual demonstration of this between SAM and other disorders: 1% of subjects were misclassified after analysis A, 5% after analysis B and 10% after analysis C. The derivation of functions in successive analyses that differ by item content and loadings is not relevant to the argument. Item loadings change markedly after subtraction or addition of subjects, since the loadings depend substantially upon the complex patterns of intercorrelations between items. The fourth criterion concerns replication with a fresh data set. This was not possible in the present study, but the classification of the 41 'ungrouped' cases provides further support of the distinction between SAM and other psychoses. The fact that none of the non-psychotic patients (15 subjects) were included in SAM is consistent with the view that the discriminant functions identified a valid boundary between SAM and other psychoses.

The analysis reported here supported the nosological status of schizoaffective mania. While this clearly requires replication, it is not an isolated finding. There are very few laboratory studies comparing subgroups of psychoses, and even fewer that separate schizoaffective disorders from others. In some biological studies where schizoaffective patients have been reported separately (sometimes by polarity), differences between schizoaffective disorder and other psychoses have been found (Meltzer *et al*, 1984); increased [^{3}H]-imipramine platelet binding in schizoaffective disorders compared with that in schizophrenia, depression, and controls (Suranyi-Cadotte *et al*, 1983), increased growth hormone response to apomorphine in schizoaffective disorders compared with that in mania (Hirschowitz *et al*, 1986), and decreased middle-ear muscle activity during REM sleep in schizoaffective disorders compared with that in schizophrenia, depression, and health (Benson & Zarcone, 1982). Marked differences between schizoaffective disorder and other diagnostic groups must argue for the retention of schizoaffective disorders as a separate category in future studies, and against the assumption that schizoaffective disorders are simply an 'interform' between schizophrenia and the affective disorders.

One of the major problems in the classification of the psychoses concerns the frequency with which disorders are encountered with features of both schizophrenia and the affective psychoses. The term 'schizoaffective' was introduced by Kasanin (1933) to distinguish good-prognosis, affect-laden schizophrenia from other schizophrenics. The schizoaffective-mania category of the RDC is a recent solution of the diagnostic problem posed by atypical psychoses with many features of mania, but with Schneider's first-rank symptoms of schizophrenia, and/or mood-incongruent hallucinations and delusions. DSM–III (American Psychiatric Association, 1980) retains the category of schizoaffective disorder only for those instances where "the clinician is unable to make a differential diagnosis with any degree of certainty". There is considerable continuing uncertainty about the existence of the schizoaffective syndrome, and this may account for there being so few biological studies on this topic (Clayton, 1982). Some authors (e.g. Pope & Lipinski, 1978) argue that the schizoaffective disorders are a subgroup of the affective psychoses, and as no consensus exists concerning the precise definition of schizoaffective disorder (Brockington & Leff, 1979; Levinson & Levin, 1987) and, according to Taylor (1984), most studies show schizoaffective disorders to be variants of the affective psychoses, unlike schizophrenia in family history, treatment response, long-term outcome, or neuropsychological and EEG findings. The existence of a distinct third type of psychosis, characterised by Langfeldt (1939) as "schizophreniform" and by Leonhard (1957) as "cycloid psychosis", may partly explain some of the uncertainty in this area. Levinson & Levin (1987) have detailed the degree of overlap between schizoaffective mania as defined by the RDC and European solutions to these problems.

It was not possible, in the present study, to determine the effect of clinical diagnostic misclassification on the interpretation of the biological data. Most studies in biological psychiatry are evaluated on the assumption that psychiatric diagnoses are free of error, but Clayton (1982) has pointed out that this is unlikely to be the case, and that schizoaffective disorders may be particularly susceptible to misclassification. The category of schizoaffective mania may include, at times, excited schizophrenics, the more severely ill manic subjects, and atypical or unclassifiable variants of the major psychoses. Kendler (1987) has argued that the effects of diagnostic misclassification should be taken into account when evaluating the results of genetic studies, and tentatively advances a mathematical model that may detect and allow for these effects. The reliability of psychiatric diagnoses, especially for those disorders where there is little agreement on diagnostic criteria, is such that misclassification rates probably seriously confound interpretation of the results.

It cannot be concluded on the basis of the results presented here that there is a subgroup of psychoses

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characterised by the features of manic disorder, with coexistent symptoms typical of schizophrenia, that is distinguishable from either schizophrenia or the affective psychoses. Our results do confirm, however, that in keeping with several recently introduced classificatory systems (and perhaps in agreement with certain European diagnostic traditions), it would be premature to discard the diagnostic category of schizoaffective disorder, especially in biological studies. In fact, the inclusion of schizoaffective patients in samples of schizophrenic or affective disorder patients may confound the results of biological investigations. The neurobiological basis of the distinction between SAM and other psychoses is unknown, and is discussed in the previous paper (Whalley *et al*, 1989). In the absence of satisfactory understanding of the neural control of the hormones that are the source of this distinction, this intriguing finding must remain unexplained.

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References

AMERICAN PSYCHIATRIC ASSOCIATION (1980) *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III). Washington, DC: APA.

BENSON, K. L. & ZARCONE, V. P. (1982) Middle ear muscle activity during REM sleep in schizophrenic, schizoaffective and depressed patients. *American Journal of Psychiatry*, **139**, 1474–1476.

BROCKINGTON, I. & LEFF, J. (1979) Schizoaffective psychosis: definitions and incidence. *Psychological Medicine*, **9**, 91–99.

BUCHSBAUM, M. B., DE LISI, L. E., HOLCOMB, H. H., *et al* (1984) Anteroposterior gradients in cerebral glucose use in schizophrenia and affective disorders. *Archives of General Psychiatry*, **41**, 1159–1166.

CLAYTON, P. J. (1982) Schizoaffective disorders. *Journal of Nervous and Mental Disease*, **170**, 646–650.

COOLEY, W. & LOHNES, P. (1971) *Multivariate Data Analysis*. New York: Wiley.

HIRSCHOWITZ, J., ZEMLAN, F. P., HITZEMANN, R. J. *et al* (1986) Growth hormone response to apomorphine and diagnosis: a comparison of three diagnostic systems. *Biological Psychiatry*, **21**, 445–454.

KASANIN, J. (1933) The acute schizoaffective psychoses. *American Journal of Psychiatry*, **13**, 97–126.

KENDELL, R. E. (1975) *The Role of Diagnosis in Psychiatry*. Oxford: Blackwell.

—— & GOURLAY, J. (1970) The clinical distinction between the affective psychoses and schizophrenia. *British Journal of Psychiatry*, **117**, 261–266.

—— & POST, F. (1973) Depressive illness in late life. *British Journal of Psychiatry*, **122**, 615–617.

KENDLER, K. S. (1987) The impact of diagnostic misclassification on the pattern of familial aggregation and co-aggregation of psychiatric illness. *Journal of Psychiatric Research*, **21**, 55–91.

KLING, A. S., METTER, J., RIEGE, W. H., *et al* (1986) Comparison of PET measurement of local brain glucose metabolism and CAT measurement of brain atrophy in chronic schizophrenia and depression. *American Journal of Psychiatry*, **143**, 175–180.

LANGFELDT, G. (1939) *The Schizophreniform States*. Copenhagen: Munksgaard.

LEONHARD, K. (1957) *Auferlung der Endogen Psychosen*. Jena: Akademie Verlag.

LEVINSON, D. F. & LEVIN, M. E. (1987) Schizoaffective mania reconsidered. *American Journal of Psychiatry*, **144**, 415–415.

MELTZER, H. Y., ARORA, R. C. & METZ, J. (1984) Biological studies of schizoaffective disorders. *Schizophrenia Bulletin*, **10**, 49–69.

MORAN, P. A. P. (1966) The establishment of a psychiatric syndrome. *British Journal of Psychiatry*, **112**, 1165–1171.

POPE, H. G. & LIPINSKI, J. F. (1978) Diagnosis in schizophrenia and manic-depressive illness: a re-assessment of the specificity of "schizophrenic" symptoms in the light of current research. *Archives of General Psychiatry*, **35**, 811–828.

RADOUCO-THOMAS, S., GARCIN, F., MURTHY, M. R. V., *et al* (1984) Biological markers in major psychoses and alcoholism: phenotypic and genotypic markers. *Journal of Psychiatric Research*, **18**, 513–539.

REIDER, R. O., MANN, L. S., WEINBERGER, D. R., *et al* (1983) Computed tomographic scans in patients with schizophrenia, schizoaffective and bipolar affective disorder. *Archives of General Psychiatry*, **40**, 735–739.

SHAGASS, C., ROEMER, R. A., STRAUMANIS, J. J., *et al* (1985) Combinations of evoked potential amplitude measurements in relation to psychiatric diagnosis. *Biological Psychiatry*, **20**, 701–722.

SIEVER, L. J., COURSEY, R. D., ALTERMAN, I. S., *et al* (1984) Impaired smooth pursuit eye movement: vulnerability marker for schizotypal personality disorder in a normal volunteer population. *American Journal of Psychiatry*, **141**, 1560–1566.

STAHL, S. M., WOO, D. J., MEFFORD, I. N., *et al* (1983) Hyperserotonemia and platelet serotonin uptake and release in schizophrenia and affective disorders. *American Journal of Psychiatry*, **140**, 26–30.

SURANYI-CADOTTE, B. E., WOOD, P. L., SCHWARTZ, G., *et al* (1983) Altered platelet [^{3}H]-imipramine binding in schizoaffective and depressive disorders. *Biological Psychiatry*, **18**, 923–927.

TAYLOR, M. A. (1984) Schizoaffective and allied disorders. In *Neurobiology of Mood Disorders* (eds R. M. Post & J. C. Ballinger). Baltimore: Williams & Watkins.

TSAI, L. Y., NASRALLAH, H. A. & JACOBY, C. G. (1983) Hemispheric asymmetries on computed tomographic scans in schizophrenia and mania: a controlled study and critical review. *Archives of General Psychiatry*, **40**, 1286–1289.

WHALLEY, L. J., CHRISTIE, J. E., BLACKWOOD, D. H. R., *et al* (1989) Disturbed endocrine function in the psychoses: I. Disordered homeostasis or disease process? *British Journal of Psychiatry*, 455–461.

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