Biological Studies of Schizoaffective Disorders

by Herbert Y. Meltzer, Ramesh C. Arora, and John Metz

Abstract

Biological studies of the relationships between the schizoaffective disorders, the affective disorders, and schizophrenia suggest that no simple reductionist model is supported by currently available data. Thus, both affective and schizoaffective patients but not schizophrenics, manifest abnormalities such as decreased platelet serotonin (5-HT) uptake, blunted clonidine-induced increase in serum growth hormone, shortened latency of rapid eye movement (REM) sleep, and increased REM density. However, there are some types of studies which show greater similarity between schizoaffective and schizophrenic patients than between schizoaffectives and affectives—e.g., increased cerebrospinal fluid (CSF) norepinephrine levels, increased platelet 5-HT content, and decreased prostaglandin E1-stimulated adenylate cyclase activity. Other types of studies show abnormalities common to all three groups of psychoses—e.g., eye tracking dysfunction, elevated CSF concentration of y-aminobutyric acid, and neuromuscular abnormalities. There are also abnormalities that have been reported to be present in only one type of the psychoses. Although none of these findings have been so unequivocally demonstrated that they can be considered to be firmly established, they do suggest that it is premature to conclude that the schizoaffective disorders are subtypes of the affective disorders. The possibility of a continuum model of the psychiatric psychoses of unknown etiology merits further consideration.

Further biological studies of a broad range of psychiatric psychoses with inclusion of the schizoaffective categories appear indicated.

Surprisingly few biological studies have been devoted to a comparison of schizoaffective disorders with the other major psychotic syndromes. This is partly due to the relatively small percentage of schizoaffective patients in most clinical populations when narrow criteria for schizoaffective illness, such as the Research Diagnostic Criteria (RDC) (Spitzer, Endicott, and Robins 1978), are used. With the use of DSM-III (American Psychiatric Association 1980), which virtually eliminates the category, full consideration of the issue is precluded unless one considers a category such as major depression with mood-incongruent delusions as a form of schizoaffective disorders. The controversy about the existence of the schizoaffective syndrome may itself preclude a specific investigation of its biology. The vigorous advocacy of classifying schizoaffective illness as a phenocopy of affective disorders by Pope and Lipinski (1978), a position adopted in DSM-III, may have caused many investigators to classify patients with mixed schizophrenic and affective symptoms as major affective disorders rather than to treat them as a separate group. The difficulty in applying any of the criteria for schizoaffective illness, even the RDC, also operates against studies designed specifically to investigate these patients in comparison with schizophrenia and affective disorders.

The purpose of this review is to examine the literature in selected areas of biological psychiatry which have been most successful in identifying putative biological abnormalities in the affective disorders, schizophrenia, or both for studies in which schizoaffective patients have

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also been included and identified. A few promising areas of research in schizophrenia or affective disorders, for which there are as yet no data on schizoaffective patients, will also be considered. The aim of the review of each research topic will be to evaluate the validity of any evidence that bears upon the issue of the biological similarities between schizophrenia, affective disorders, and schizoaffective disorders. It is apparent that the validity of this evidence depends on many factors, including at the minimum: (1) competence in the process of diagnostic assessment; (2) diagnostic criteria; (3) reliability of biological determination; (4) sample size; and (5) statistical analysis. Although the evidence is too fragmentary for definitive conclusions, there are already enough data to clarify the broad outlines of these relationships.

Noradrenergic Measures

One of the major theories of the etiology of depression has been the so-called catecholamine hypothesis of depression, i.e., that there is a functional decrease in the activity of noradrenergic neurons in some type of major depressive illness (Schildkraut 1965; Bunney and Davis 1965). More recently, on the basis of evidence that chronic administration of a variety of antidepressant drugs and electroconvulsive treatment decrease the functional activity of β-adrenergic receptors, Sulser, Vetulani, and Mobley (1978) have proposed that there might be a functional increase in noradrenergic activity in major depression before treatment. There has also been considerable interest in the role of norepinephrine (NE) in schizophrenia in recent years. Early studies suggested the possibility of decreased noradrenergic activity based upon a decrease in brain dopamine-β-hydroxylase activity (Stein and Wise 1971), but this finding could not be confirmed (Wyatt et al. 1975). Recently, various types of evidence have suggested that there might be an increase in noradrenergic activity in some forms of schizophrenia, especially paranoid schizophrenia. For example, increased levels of NE in the brains of deceased paranoid schizophrenics (Farley et al. 1978; Crow et al. 1979) and increased levels of NE in the cerebrospinal fluid (CSF) of schizophrenic patients have been reported (Lake et al. 1980; Sternberg et al. 1981). There is indirect evidence that β-adrenergic activity may be of some importance in schizophrenia in that numerous reports suggest at least some schizophrenic patients respond favorably to high doses of the β-adrenergic blocker, propranolol (Atsmon et al. 1971, 1972; Yorkston et al. 1974; Elizur et al. 1979; Lindstrom and Persson 1980). However, other controlled studies fail to report a beneficial effect of propranolol in chronic schizophrenia (Myers et al. 1981; Peet et al. 1981). Because of the evidence for a role of NE in both depression and schizophrenia, it is of interest to examine the possibility of an abnormality of NE in the schizoaffective disorders.

3-Methoxy-4-Hydroxyphenylglycol. Decreased levels of urinary 3-methoxy-4-hydroxyphenylglycol (MHPG), the major metabolite of NE, have been reported in various subtypes of major depression (Maas, Dekirmenjian, and Fawcett 1974) and have been proposed to be useful in identifying patients who respond best to drugs which supposedly have some specificity for increasing noradrenergic activity, e.g., imipramine or nortriptyline (Maas, Fawcett, and Dekirmenjian 1972; Maas 1975; Hollister, Davis, and Berger 1980). There is, in fact, scant evidence that these drugs are selective noradrenergic potentiators in vivo; nevertheless, the finding of an association between low MHPG in urine and good clinical response to these or other antidepressant drugs has been surprisingly robust (Maas, Fawcett, and Dekirmenjian 1972; Beckmann and Goodwin 1975; Rosenbaum et al. 1980; Maas et al. 1982), although there have been negative results (Spiker et al. 1980). There are as yet no data on whether urinary MHPG is as effective a predictor of response to specific antidepressants in schizoaffective patients as in affective patients.

Urinary MHPG has been found to be low in some schizophrenic patients (Schildkraut et al. 1978b; Taube et al. 1978) but not in groups of schizophrenics compared to normal controls (Joseph et al. 1976; Taube et al. 1978).

Originally, MHPG in urine was thought to arise at least 60 percent from brain, but more recent studies have demonstrated that it is largely peripheral in origin (Izzo, Horwitz, and Keiser 1979; Blombery et al. 1980). Despite this, it is still of interest to determine if MHPG in urine differs in subgroups of psychiatric patients since a peripheral abnormality may reflect a comparable central abnormality or it may simply be a biological correlate of psychopathology. Thus, Deakin et al. (1979) found a significant negative correlation between severity of illness and measures of arousal and urinary MHPG in a group of chronic schizophrenics. Schildkraut et al. (1978b) reported that 24-hour urinary MHPG was significantly lower in four schizoaffective depressed patients (depressed patients with psychotic manifestations that were not solely affect consonant but without histories
of chronic asocial behavior) and 11 bipolar depressed patients than in 13 unipolar nonendogenous depressed patients. They also found that nine patients diagnosed as schizophrenic-related depression (patients with schizophrenia, depressive symptoms, and chronic asocial behavior) had lower urinary MHPG than the unipolar nonendogenous depressed patients.

Beckmann and Goodwin (1980) also reported the urinary MHPG in five unmedicated schizoaffective depressed patients (RDC, subtype not specified) was significantly lower than that of normal controls and unipolar depressed patients but comparable to that of bipolar depressed patients. Thus, at least two studies have found low MHPG in the urine of schizoaffective depressed patients and bipolar patients, but the implications this finding has for the relationship of schizoaffective depression to affective disorders is unclear because of the small size of the samples, differences in diagnostic criteria, and the evidence that at least some schizophrenic patients may have decreased urinary MHPG excretion as well. The greater differentiation of bipolar depressed patients from unipolar patients rather than from schizoaffective patients is worthy of note. Genetic studies have also suggested schizoaffective illness is closer to bipolar illness than unipolar illness (Mendlewicz, Linkowski, and Wilmotte 1980). Further studies of urinary MHPG, as well as plasma and CSF MHPG, in a full spectrum of psychotic patients with affective or schizophrenic symptoms, or both, under the controlled conditions necessary to obtain reliable information in this difficult area of research would seem indicated.

Plasma and CSF Norepinephrine.

There have been a few studies of plasma and CSF NE concentrations in the major affective disorders, schizophrenia, and schizoaffective disorders. Supine, resting plasma levels of NE were significantly positively correlated with CSF NE concentrations in one study (Lake et al. 1982b) but not in another (Kemali, Del Vecchio, and Maj 1982). Plasma NE concentration may reflect sympathetic nervous activity, while the CSF NE concentration may reflect central noradrenergic activity (Wood 1980).

Lake et al. (1982a, 1982b) found that patients with major affective disorder (manic, unipolar, and bipolar depressed) had elevated plasma NE compared to normal controls. These investigators (Lake et al. 1982b) also found that plasma NE values in 10 schizoaffective patients (RDC, subtype unspecified) and chronic schizophrenics did not differ from those in normal controls. However, Ackenheil et al. (1980) and Kemali, Del Vecchio, and Maj (1982) reported elevated plasma NE in acute and chronic schizophrenia. The plasma NE levels in the controls were similar in the three studies. The explanation of the discrepancies is not known. It could reflect the effect of stress.

Increased CSF NE concentrations have been reported in schizophrenic patients in four studies (Gomes et al. 1980; Lake et al. 1980; Sternberg et al. 1981; Kemali, Del Vecchio, and Maj 1982). However, Gattaz et al. (1983) found no difference in CSF NE between unmedicated schizophrenics and normal controls. Patients receiving neuroleptics showed significantly higher CSF levels of NE. They suggested that these results could be due to the effect of neuroleptic drugs. However, in the studies of Lake et al. (1980) and Sternberg et al. (1981), patients were drug free for 2 weeks. Moreover, pimozide treatment was found to decrease NE concentration in CSF. Therefore, it is quite possible that the elevation of NE in the CSF of schizophrenic patients is not a drug-treatment artifact. There have been no published studies of CSF NE in major depression to our knowledge. Sternberg et al. (1981) reported that CSF NE was as elevated in nine schizoaffective patients (RDC, schizophrenic subtype) as in 24 schizophrenic patients without affective features. Although no significant correlations between CSF NE levels and severity of psychosis, length of illness, or length of hospitalization were found, they did observe a significant correlation between the decrease in CSF NE levels in pimozide-treated patients and decrease in psychosis ratings. On the other hand, CSF NE levels remained elevated in five patients whose psychoses remitted without drug treatment. These findings further support a role of NE in schizophrenia and the mechanism of action of neuroleptic drugs. They also support the possibility of a biological overlap between some forms of RDC schizoaffective illness, schizophrenic subtype and schizophrenia. Data on CSF NE in RDC schizoaffective disorder, affective subtypes, and major affective illness should be of considerable interest.

Effect of Clonidine on Plasma MHPG, Blood Pressure, and Growth Hormone. Sternberg et al. (1982) further explored the causes of elevated NE in plasma and CSF of schizoaffective patients by investigating the ability of clonidine, an α-adrenergic agonist, to lower plasma levels of MHPG and blood pressure. The decrease in plasma MHPG due to clonidine is believed to reflect stimulation of central presynaptic α-adrenergic receptors (Charney et al.
1981). It is not clear whether the hypotensive action of clonidine is due to stimulation of presynaptic or postsynaptic \( \alpha_1 \)-adrenergic receptors (Charney et al. 1982). Seven schizophrenic and four schizoaffective patients (RDC, mainly schizophrenic subtype) were compared to 11 age-matched normal controls. The decrease in MHPG produced by clonidine was blunted in both the schizophrenic and schizoaffective depressed patients (Sternberg et al. 1982). This group subsequently reported no difference in the decrease in plasma MHPG in 15 depressed patients (2 bipolar, 13 unipolar) and 12 normal controls. The decrease in blood pressure produced by clonidine did not differ between either group of patients and controls. The clonidine-induced fall in blood pressure is also not decreased in unmedicated depressed patients (Checkley, Slade, and Shur 1981; Charney et al. 1982). These MHPG results, like the CSF and plasma NE data, suggest that RDC schizoaffective depression, mainly schizophrenic patients, may be more closely related to schizophrenia than to major depression.

Matussek et al. (1980) examined the ability of clonidine (0.1 mg i.v.) to stimulate growth hormone secretion in endogenous and neurotic depression, schizophrenia, schizoaffective psychoses (ICD-8 295.7) and normal controls. The patients with schizoaffective psychoses had manic or depressive symptoms mingled with paranoid-hallucinating symptoms which predominated. Both the endogenous depressed and schizoaffective patients had a blunted growth hormone response compared to the controls and neurotic depressed patients. Schizophrenics had an elevated growth hormone response to clonidine. Matussek et al. (1980) suggested that these results indicate that the blunted growth hormone response in schizoaffective disorders may be an indication that this disorder is more closely related to endogenous depression and affective disorders than to schizophrenia. The blunted growth hormone response to clonidine in depression compared to schizophrenia has also been observed by Checkley, Slade, and Shur (1981), Siever et al. (1982a, 1982b), Charney, Heninger, and Sternberg (1982), and Charney et al. (1982). Further studies of the clonidine-induced increase in growth hormone in schizoaffective depressed patients are clearly indicated. If it is confirmed that a blunted growth hormone response is present in both schizoaffective depressed patients and major depression, this would indicate a common pathophysiologic abnormality, i.e., \( \alpha_1 \)-adrenergic subsensitivity, if not a common etiology.

**Serum Dopamine-\( \beta \)-Hydroxylase Activity and Catechol-O-Methyl Transferase Activity.** Serum dopamine-\( \beta \)-hydroxylase (DBH) has been extensively studied in schizophrenia and the affective disorders. Brain DBH activity could conceivably be relevant to the putative catecholamine abnormality in these disorders since DBH catalyzes the conversion of dopamine (DA) to NE. A deficiency in DBH might lead to enhanced DA levels in noradrenergic neurons and a deficiency of NE. Serum DBH activity is under genetic control (Ross, Wetterberg, and Myrhed 1973; Weinshilboum et al. 1973). Meltzer et al. (1976) reported decreased serum DBH activity in patients with schizophrenia, mania, and抑郁性精神病, and normal controls (table 1). Serum DBH activity was determined as previously described (Meltzer et al. 1976). No significant differences were found. Gershon et al. (1980) also found no significant differences in serum DBH activity in seven schizoaffective patients (RDC, subtype not specified) and large groups of bipolar and unipolar depressed patients, and normal controls.

Gershon et al. (1980) found no differences in the activity of red cell catechol-O-methyltransferase, the enzyme which converts NE to epinephrine, among schizoaffective patients, major affective disorders, and normal controls.

**\( \alpha_1 \)-Adrenergic Receptors in Platelets.** Kafka, Van Kammen, and Bunney (1979) examined the density of \( \alpha_1 \)-adrenergic binding sites in blood platelets of schizophrenics (\( n = 11 \)), schizoaffectives, criteria not specified (\( n = 9 \)), and normal controls (\( n = 38 \)). No significant differences were found. However, the ligand used in that study, \(^{3}H\)-dihydroergocriptine (DHE), is not specific for \( \alpha_1 \)-adrenergic receptors. In a subsequent study using \(^{3}H\)-yohimbine as a ligand, U’Prichard et al. (1982) reported an increased number of \( \alpha_1 \)-
adrenergic binding sites in the blood
platelets of four schizoaffective
patients (RDC, depressed, mainly
affective) compared to normal
controls, major affective disorders,
and schizophrenic patients.

Subsequently, Kafka and Van
Kammen (1983) also reported
increased numbers of platelet \( \alpha_2 \)-receptors in 14 schizoaffective
patients, mainly schizophrenic using
\( ^3 \text{H-DHE} \) as ligand, but they did not
specify whether they were comparing
the schizoaffective patients to normal
controls or schizophrenics, or both.
Inspection of their data suggests the
schizoaffective patients may have
had higher levels than both the
schizophrenics and controls. Thus,
the data from U'Prichard et al. (1982)
and Kafka and Van Kammen (1983)
suggest that platelet \( \alpha_2 \)-adrenergic
receptor density may be uniquely
elevated in schizoaffective patients.
However, many more patients need
to be studied.

Techniques for assessing peripheral
\( \alpha_2 \) receptors are still developing. In
addition to the ligand density
measure, it will be of interest to
determine if there is any abnormality
in the coupling of the neurotrans-
mittor to adenylate cyclase.

### Dopaminergic Measures

**CSF Dopamine Metabolites.** CSF
concentrations of homovanillic acid
(HVA) in schizophrenia, mania, and
depression have not revealed
conclusive evidence of either
increased or decreased dopamine
turnover (Meltzer and Stahl 1976;
Cowdry and Goodwin 1978).

found no difference in CSF HVA
concentrations in 30 schizophrenic,
31 schizoaffective, and 41 patients
with major affective disorders. They
did note a significant negative correlation
between premorbid sexual
adjustment and CSF HVA in the
schizophrenic patients but not the
other two diagnostic groups. Bowers
and Heninger (1981) reported the
development of tolerance to neuro-
leptic-induced increases in CSF HVA
in both schizophrenics and schizo-
affectives.

**Dopamine Agonist Effects on
Pituitary Hormone Secretion.** Neuro-
endocrine measures of the dopamin-
ergic system include assessment of
the apomorphine-induced increase in
growth hormone (GH) or decrease in
serum prolactin (PRL). Apomorphine
has a direct action at dopamine
receptors in the hypothalamus which
stimulate GH release via release of
hypothalamic peptides such as
growth hormone releasing factor and
at the pituitary to inhibit PRL release
directly (Meltzer, Busch, and Fang
1981). The mean GH or PRL
response to apomorphine does not
differentiate among schizophrenics,
affectives, and schizoaffective
patients (RDC, both subtypes)
(Meltzer et al., in press). However,
an exaggerated GH response (GH
area under the curve > 100 units),
the cutoff point suggested by
graphical evidence of bimodality,
was less common in a combined
group of schizoaffective depression,
primarily affective, and major
depression than in the combined
group schizophrenia, mania, schizo-
affective depression, primarily
schizophrenic, and schizoaffective
mania (1 of 26 vs. 17 of 71,
\( x^2 = 5.09, p = 0.024 \)). Other
investigators have found blunted PRL
responses in chronic schizophrenics
(Tamminga et al. 1977) and increased
responses in acute schizophrenics
(Pandey et al. 1977). Maany et al.
(1979) reported no abnormality in
the apomorphine-induced GH
response in depression.

### Serotonergic Measures

**Platelet Serotonin Uptake.** Serotonin
(5-HT) is actively taken up by a
concentration-dependent, energy-
requiring process into blood platelets.
Decreased active uptake of 5-HT by
platelets of unmedicated unipolar and
bipolar depressed patients has been
reported in many studies (Hallstrom
et al. 1976; Tuomisto and Tukiainen
1976; Coppen, Swade, and Wood
1978; Scott, Reading, and Louden
1979; Tuomisto, Tukiainen, and
Ahlfors 1979; Ross et al. 1980;
Aberg-Wistedt et al. 1981; Meltzer et

<table>
<thead>
<tr>
<th>Diagnostic groups</th>
<th>n</th>
<th>Serum DBH activity</th>
<th>( \mu \text{mole/minute/liter} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>41</td>
<td>16.7 ± 12.9</td>
<td></td>
</tr>
<tr>
<td>Psychotic depression</td>
<td>42</td>
<td>18.4 ± 14.4</td>
<td></td>
</tr>
<tr>
<td>Schizophrenic depression</td>
<td>27</td>
<td>19.0 ± 13.4</td>
<td></td>
</tr>
<tr>
<td>Mainly affective, others</td>
<td>20</td>
<td>20.0 ± 15.7</td>
<td></td>
</tr>
<tr>
<td>Mainly schizophrenic</td>
<td>19</td>
<td>17.9 ± 12.6</td>
<td></td>
</tr>
<tr>
<td>Mania</td>
<td>14</td>
<td>19.5 ± 10.4</td>
<td></td>
</tr>
<tr>
<td>Schizoaffective mania</td>
<td>8</td>
<td>14.5 ± 9.7</td>
<td></td>
</tr>
<tr>
<td>Mainly affective, others</td>
<td>8</td>
<td>18.9 ± 10.2</td>
<td></td>
</tr>
<tr>
<td>Mainly schizophrenic</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1\(^{\text{Mean ± SD.}}\)
This effect is due to a decrease in the number of serotonin uptake sites ($V_{\text{max}}$). There appears to be no increase in the number of uptake sites after recovery (Coppen, Swade, and Wood 1980). We have obtained similar data (H.Y. Meltzer, A. Kantor, and R.C. Arora, unpublished data).

Meltzer et al. (1981), Meltzer, Arora, and Song (1982), Arora and Meltzer (1982), and Stahl et al. (1983) reported no decrease in 5-HT uptake by blood platelets of schizophrenic patients, but an Israeli group has found a significant decrease in platelet 5-HT uptake in acute schizophrenic patients (Modai et al. 1979; Rotman et al. 1979, 1980, 1982).

Schizoaffective depressed patients, mainly affective, were reported to have significantly decreased platelet 5-HT uptake whereas schizoaffective depressed, mainly schizophrenic, patients did not (Meltzer, Arora, and Song 1982). There were too few schizoaffective manic patients studied to determine their uptake relative to that of manic patients, which was not decreased. Stahl et al. (1983) reported normal platelet 5-HT uptake in eight patients diagnosed as schizoaffective depressed. However, the subtype was not described. Both Meltzer, Arora, and Song (1982) and Stahl et al. (1983) used RDC criteria.

We have now studied platelet 5-HT uptake, using a previously described method (Meltzer, Arora and Song 1982), in additional patients and controls (table 2). There was a significant difference between groups ($F = 10.60; df = 4, 244, p < .0001$). Post hoc tests demonstrated significantly lower $V_{\text{max}}$ in patients with major depression and schizoaffective depression, mainly affective or other compared to normal controls, schizophrenics, and schizoaffective depressed, mainly schizophrenic.

These data suggest that RDC schizoaffective depressed, mainly affective, or other are similar to major depressions and can be differentiated from schizophrenics and schizoaffective depressed, mainly schizophrenic, on the basis of this biological measure. Platelet 5-HT uptake may reflect brain 5-HT uptake and could be relevant to the hypothesis of decreased 5-HT in the affective disorders.

**Platelet Serotonin.** Platelet 5-HT content has been extensively studied because it is one of a number of parameters of 5-HT physiology in the platelet which might be informative concerning brain serotonergic abnormalities in psychiatric disorders. Platelets do not synthesize serotonin. They incorporate 5-HT as they are formed, have the capacity to take up 5-HT by an active process as well as passive diffusion, store 5-HT in granules, release 5-HT and probably metabolize it via monoamine oxidase (MAO), even though 5-HT is a relatively poor substrate for the type of MAO, MAO B, present in platelets (Sneddon 1973).

Schizophrenic patients have been reported to have elevated platelet 5-HT in a number of studies (Todrick, Tair, and Marshall 1960; Garelis et al. 1975; Delisi et al. 1981; Freedman et al. 1981; Jackman, Luchins, and Meltzer 1983; Stahl et al. 1983). On the other hand, most studies have reported significantly lower platelet 5-HT levels in major depression compared to normal controls (Sarai and Kayano 1968; Coppen et al. 1976b; Takahashi 1976; Banki 1978; Banki and Vojnik 1978). Normal levels were reported in bipolar depressed patients by Kaneko et al. (1975) and by Jackman, Luchins, and Meltzer (1983), and in unipolar patients by Wirz-Justice and Puhringer (1978), who also reported elevated platelet 5-HT in manic patients.

Platelet 5-HT concentration in schizoaffective patients has been found to be nonsignificantly higher than that of normal controls in three studies (Joseph et al. 1977; Jackman, Luchins, and Meltzer 1983; Stahl et al. 1983). Jackman, Luchins, and Meltzer (1983) found that platelet 5-HT levels in schizoaffective depressed, mainly schizophrenic patients were higher than those of controls and comparable to those of schizophrenics, which were also elevated. On the other hand, schizoaffective depressed, mainly affective patients had platelet 5-HT levels lower than normal controls.

**Table 2.** $V_{\text{max}}$ of platelet 5-HT uptake in diagnostic groups

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>$n$</th>
<th>$V_{\text{max}}$ (pmoles/10^7 platelets/minute)</th>
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<tbody>
<tr>
<td>Controls</td>
<td>52</td>
<td>12.3 ± 2.7</td>
</tr>
<tr>
<td>Major depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unipolar psychotic</td>
<td>22</td>
<td>8.5 ± 3.2</td>
</tr>
<tr>
<td>Bipolar psychotic</td>
<td>26</td>
<td>6.8 ± 2.7</td>
</tr>
<tr>
<td>Schizoaffective depressions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mainly affective, others</td>
<td>20</td>
<td>9.8 ± 2.4</td>
</tr>
<tr>
<td>Mainly schizophrenic</td>
<td>23</td>
<td>10.7 ± 4.3</td>
</tr>
<tr>
<td>Schizophrenic</td>
<td>85</td>
<td>10.9 ± 3.8</td>
</tr>
</tbody>
</table>

$F = 10.66; df = 4, 244; p < .0001.$

$'p < .05$ compared to normal controls.
comparable to those of normal controls and patients with major depression. The latter two studies used the RDC to diagnose patients whereas Joseph et al. (1977) used Catego. The fact that relatively small numbers of subjects were included in each of the studies no doubt contributed to the failure to find significance. A power analysis of the data with acutely ill schizoaffective patients of Joseph et al. (1977) suggests that a sample size of approximately 25 such patients and controls would be necessary to have a 90 percent probability of identifying a difference between the schizoaffective depressed patients and normal controls. None of the three studies approached this sample size. The variance within groups was quite large in all subjects, suggesting that elevated platelet 5-HT may be characteristic of only some schizoaffective patients (e.g., those with mainly schizophrenic symptomatology) and that variables not controlled for in the study, such as diet and endocrine status, may affect 5-HT levels in platelets. Thus, these data suggest that, with regard to platelet 5-HT levels, schizoaffective patients more closely resemble schizophrenics than affective disorders.

Tueting and Meltzer (unpublished data) have recently found a significant negative correlation between platelet 5-HT concentration and platelet MAO activity in a group of 33 unmedicated newly hospitalized patients with primary affective disorder, including 10 schizoaffective patients, mainly affective (RDC). For the 10 schizoaffective patients, the correlation was also significant ($r = - .683, p < .03$). On the other hand, the correlation between these variables for schizoaffective, mainly schizophrenic patients was .07 ($n = 7$) and for schizophrenics ($r = .296, n = 22, p = .18$). Thus, the relationship between these variables was quite different for the two subtypes of schizoaffective patients. The correlation was also significant and negative for normal controls ($r = - .506, n = 19, p < .03$). These results will be presented in detail elsewhere. They point toward a relationship between 5-HT and MAO in the platelet, and perhaps the brain, since there is increasing evidence that MAO-B in brain has an important role in 5-HT physiology (Squires and Lassen 1975; Levitt, Pintar, and Breakefield 1982) and the platelet may be a model for brain 5-HT uptake and storage. The group differences just reported suggest that the primarily affective subtype of RDC schizoaffective disorder more closely resembles primary affective disorder, whereas the primarily schizophrenic subtype is more similar to schizophrenia.

**Platelet Monoamine Oxidase Activity.**

Because of early reports of decreased platelet MAO activity in both depression (Murphy and Weiss 1972) and schizophrenia (Wyatt et al. 1973), MAO activity has been one of the most intensively investigated biochemical parameters in these disorders. Studies of platelet MAO in depressed patients were reviewed by Coper et al. (1979), who noted five studies reporting increased platelet MAO activity in endogenous depression, four reporting decreased MAO activity, and seven, including their own, which found no difference in platelet MAO activity between endogenous depression and controls. Murphy et al. (1982) suggested that some of the discrepancy between studies of platelet MAO in depression was due to failure to distinguish between primary (unipolar and bipolar) and secondary affective disorders. They suggested that unipolar and secondary depressions are most likely to have increased platelet MAO activity whereas bipolar patients are most likely to have decreased platelet MAO activity. Since that review, the literature concerning platelet MAO in depression remains as conflicting: Maubach et al. (1981) and Meltzer et al. (1980) found no difference; Mann (1979), White et al. (1980), and Murphy et al. (1982) found increased platelet MAO activity; and Puzynski, Hauptmann, and Zaluska (1983) found decreased platelet MAO activity in major depression compared to controls. The discrepancies between these studies may be the result of differences in diagnostic assessment, subtypes of depression represented in the sample, nature of control groups, failure to account for sex differences including the effect of menopausal status, age differences, methods of platelet preparation, and methods of determination of platelet MAO activity.

The literature in regard to platelet MAO in schizophrenia is slightly less conflictual than that with regard to depression. Most studies have reported decreased platelet MAO activity or no difference (Wyatt, Potkin, and Murphy 1979). There is strong evidence that the decreased platelet MAO activity observed in many groups of schizophrenic patients resulted from neuroleptic treatment (DeLisi et al. 1981; Meltzer et al. 1980).

There are only a few studies of platelet MAO activity in schizoaffective disorder. SchilDKraut et al. (1978a) found increased platelet MAO activity in patients with depressive disorder accompanied by a history of chronic asocial, eccentric, or bizarre behavior, a group referred to as schizophreniarelated depressive disorders. Brockington et al. (1976) studied a group
of 55 patients diagnosed as schizo-affective who met the criteria for schizophrenia or paranoid psychoses as well as a manic or depressive psychosis. Female schizo-affectives had higher platelet MAO activity than schizophrenics or controls, but male schizo-affectives were not different from male controls or schizophrenics. In a subsequent study from this group, Joseph et al. (1977) reported increased platelet MAO activity in eight acutely ill male schizoaffective patients compared to 13 recovered schizoaffective patients. Van Kammen et al. (1978) studied schizoaffective patients, had the best difference in platelet MAO activity for female improvers was lower than admission. Platelet MAO activity of partially or completely during a 30-day drug-free period following admission. Platelet MAO activity of female improvers was lower than that of normal controls, but no difference in platelet MAO activity of all schizo-affectives (n = 16) and schizophrenics (n = 6) was found. Malas and Van Kammen (1983) recently published a followup study on these and additional patients and found that patients in the lowest one-third of MAO activity, including five schizo-affective patients, had the best social functioning.

In table 3, our data on the platelet MAO activity of male and female normal controls, and unmedicated schizo-affectives, manic and depressed, primarily affective or schizophrenic, and chronic schizophrenic patients using 14C-benzylamine as substrate are presented. Platelet MAO activity was measured as previously described (Jackman and Meltzer 1980). Some of these results have been previously reported (Meltzer, Perline, and Lewine 1982; Meltzer, Tueting, and Jackman 1982). There were no significant differences among any of the groups.

Thus, it appears unlikely that platelet MAO activity per se will be useful in clarifying the relationship between the three types of psychotic symptoms. The most intriguing finding may be the unpublished data of Tueting and Meltzer reviewed in the previous section concerning the differences in the correlation between platelet 5-HT and platelet MAO between affective and schizophrenic patients. This observation has to be replicated by independent investigators.

Spinal Fluid Tryptophan. Bowers and Heninger (1977) examined CSF tryptophan levels before and after lithium treatment in seven schizophrenics. In a subsequent study (Jackman and Meltzer 1980). Some of these results have been previously reported (Meltzer, Perline, and Lewine 1982; Meltzer, Tueting, and Jackman 1982). There were no significant differences among any of the groups.

Table 3. Platelet MAO activity in normal controls, schizoaffectives, chronic schizophrenia, and psychotic depression

<table>
<thead>
<tr>
<th>Group</th>
<th>Platelet MAO activity (nmole*14C-benzaldehyde/hour/10^6 platelets)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males n</td>
</tr>
<tr>
<td>Normal controls</td>
<td>9.7 ± 2.6</td>
</tr>
<tr>
<td>Schizoaffective</td>
<td></td>
</tr>
<tr>
<td>depressed</td>
<td></td>
</tr>
<tr>
<td>Mainly affective</td>
<td>9.5 ± 4.2</td>
</tr>
<tr>
<td>Mainly schizophrenic</td>
<td>9.0 ± 4.3</td>
</tr>
<tr>
<td>Schizophrenic</td>
<td>10.5 ± 3.5</td>
</tr>
<tr>
<td>Psychotic depression</td>
<td>8.4 ± 4.0</td>
</tr>
</tbody>
</table>

$\gamma$-Aminobutyric acid (GABA) levels have been measured in CSF as a crude index of brain GABAergic activity. There are conflicting results concerning the concentrations of GABA in schizophrenia and affective disorders, but some investigators have reported low levels in drug-free schizophrenics (Van Kammen, Sternberg, and Hare 1981) and depressed patients (Gerner and Hare 1981). There have been three studies of CSF GABA levels in schizoaffective patients. Gold et al. (1980) found low CSF GABA levels in five schizo-affective patients (RDC, subtype not specified) and in 15 patients with major depression compared to 20 controls. The seven schizophrenics they studied had normal CSF GABA. Sternberg, Van Kammen, and Hare (1980) and Van Kammen et al. (1982) did not find low CSF GABA in small groups of schizoaffective patients (RDC, subtype not specified). It would seem worthwhile to continue the investigation of CSF GABA in a suitably large and subdivided group of schizoaffective patients.

Viral Antibodies and Immunoglobulins

There is considerable interest in the
possibility that schizophrenia, or at least some forms of it, might be due to an autoimmune process or to viral infections (Torrey and Peterson 1973, 1976; Tyrell et al. 1979). We have reviewed this evidence elsewhere (Meltzer 1979). Torrey et al. (1978) explored the possibility of a viral etiology in schizophrenia, schizo-affective disorder, and manic-depressive disorder by investigating the ratio of viral antibodies in serum and CSF. The normal serum/CSF ratio for measles antibody is > 200. It has been suggested that values below 160 might indicate abnormalities of the blood-brain barrier or production of antibody in the central nervous system (CNS). Four of 80 patients with neurological disorder, 3 of 30 multiple admission schizophrenics, and 1 of 9 schizoaffective patients (RDC criteria, subtype not specified) had ratios > 160. No abnormalities were found in 14 manic depressives, 13 first admission schizophrenics, or 10 normal controls. No abnormalities suggestive of previous rubella, herpes simplex, or cytomegalovirus were found. CSF IgG was abnormally elevated in a few of the multiple admission schizophrenics and some of the manic-depressive patients but none of the schizoaffectives. These limited data are inconclusive about the relationship of viral infections to schizoaffective disorder or the relationships among schizophrenic, affective, and schizoaffective disorders.

**Neuroendocrine Studies**

**Dexamethasone Suppression Test.** The dexamethasone suppression test (DST) has been extensively studied in major depression as a means of identifying patients with abnormalities of the hypothalamic-pituitary-adrenal axis. The majority of studies have found that 30-50 percent of patients with major depression fail to suppress serum cortisol at 4 a.m. and 11 p.m. the day after receiving dexamethasone 1 mg at 11:30 p.m. (Carroll 1982; Holsboer, Liebl, and Hofschuster 1982). Unipolar depressed and bipolar depressed patients with psychotic symptoms have been reported to have a higher incidence of abnormal dexamethasone suppression tests than nonpsychotic patients (Mendlewicz, Charles, and Franckson 1982; Rothschild et al. 1982; Caroff et al. 1983). Most studies find a low incidence of nonsuppression in schizophrenia (Carroll, Curtis, and Mendels 1976; Schlesser, Winokur, and Sherman 1980; Meltzer et al. 1982), but one recent study reported that 6 of 20 chronic schizophrenics were nonsuppressors (Dewan et al. 1982). Manic patients have been reported to suppress normally in some studies (Carroll 1979; Schlesser, Winokur, and Sherman 1980), but the latter used only 8 a.m. postdexamethasone samples. Graham et al. (1982) reported that 23 of 50 (46 percent) manic patients were nonsuppressors with the 2 mg dexamethasone suppression test. Stokes et al. (1976) reported that three of nine schizoaffective patients diagnosed using DSM-II criteria were nonsuppressors compared to 27 of 59 (46 percent) depressed patients and 5 of 29 (17 percent) schizophrenic patients. Thus, the schizoaffective patients were intermediate with regard to the DST.

Surprisingly, there have been no published studies of the DST in schizoaffective disorder diagnosed according to RDC. Carroll (1982) reported his own unpublished data that "schizoaffective depressed (by RDC) have the same high frequency of abnormal DST results as do ordinary melancholics." He cites similar unpublished conclusions from Carman et al. and also from Schlesser, Winokur, and Sherman (1980). Rothschild et al. (1982) reported that only one of four schizoaffective patients (DSM-III criteria) was a nonsuppressor. Targum et al. (1983) reported on a group of 17 schizophreniform patients (DSM-III) who at followup were rediagnosed as schizophrenia (n = 7) or as possible major depression (n = 10). Some of the latter patients would likely meet RDC for schizoaffective depression. Three of the 10 "schizoaffective" patients had an abnormal DST compared to one of the seven schizophrenic patients.

Our data from the 1 mg overnight DST with sampling at 8 a.m. and 4 p.m. and use of a radioimmunoassay to determine serum cortisol are given in table 4. The incidence of nonsuppression (serum cortisol > 5 μg/dl in 8 a.m. or 4 p.m. sample) was significantly greater in major depression than in normal controls. This was not so for any other group. However, 28.6 to 33.3 percent of schizoaffective depressed and schizoaffective manic patients were nonsuppressors; if these groups are combined, the incidence of nonsuppression (10/33, 30.3 percent) approaches being significantly greater than that of normal controls (χ² = 3.12, p < .10) but less than that of major depression (χ² = 2.94, p < .10). At this point in our data acquisition, it appears that the incidence of DST nonsuppression in schizoaffective patients is intermediate between that of major depression and schizophrenia or mania. These results are similar to those reported by Stokes et al. (1976).

**Response to Thyrotropin-Releasing Hormone.** A number of investigators have reported that unipolar and
Table 4. Sensitivity of dexamethasone suppression test in schizoaffective patients and other groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Total n</th>
<th>Nonsuppression</th>
<th>% Nonsuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizoaffective, depressed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primarily affective</td>
<td>14</td>
<td>4</td>
<td>28.6</td>
</tr>
<tr>
<td>Primarily schizophrenic</td>
<td>12</td>
<td>4</td>
<td>33.3</td>
</tr>
<tr>
<td>Schizoaffective manic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primarily affective</td>
<td>7</td>
<td>2</td>
<td>28.6</td>
</tr>
<tr>
<td>Major depression</td>
<td>53</td>
<td>26</td>
<td>49.1</td>
</tr>
<tr>
<td>Mania</td>
<td>16</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>36</td>
<td>7</td>
<td>19.4</td>
</tr>
<tr>
<td>Normal controls</td>
<td>21</td>
<td>2</td>
<td>9.5</td>
</tr>
</tbody>
</table>

Bipolar patients have an increased frequency of blunted thyroid-stimulating hormone (TSH) responses to a standard dose of thyrotropin-releasing hormone (TRH) (for references, see Loosen and Prange 1982). Schizoaffective patients do not have blunted TSH responses following TRH (Prange et al. 1979; Loosen and Prange 1980; Extein et al. 1982). There have been, to our knowledge, two published studies of the TSH response to TRH which included schizoaffective patients. Loosen and Prange (1980) included 5 schizoaffective patients (RDC criteria) in a group with 12 schizophrenics so the schizoaffectives may have been the mainly schizophrenic subtype. All had normal TSH responses. Gold et al. (1981) studied 5 schizoaffective depressed and 10 schizoaffective manic patients (RDC, subtype not specified). None of the depressed and 3 of the manic subtypes had blunted responses. The low rate in schizoaffective depressed patients was comparable to that of bipolar depressed patients but much less than that of unipolar patients. The rate of blunted responses in schizoaffective manics was comparable to that in manic patients. Targum et al. (1983) in the study previously described reported that 5 of 10 possible schizoaffective patients had a blunted TSH response compared to none of the 7 schizophrenic patients. However, the TSH responses were between 5 and 7 

μU/ml in three of the five patients with blunted responses. The small number of subjects in the three published studies, as well as the results we have obtained, and the uncertainty as to the subtypes of schizoaffective patients in the studies of Loosen and Prange (1980) and Gold et al. (1981) make it impossible to ascertain whether the TSH response to TRH is informative about the relationship between schizoaffective disorders and the "purer" psychotic syndromes. Additional studies with a larger number of subjects and specification of subtypes of schizoaffective patients appear indicated.

Cyclic Adenosine Monophosphate Production in Blood Platelets

There have been several studies of cyclic nucleotide production in the blood platelets of schizophrenic patients. These have generally reported decreased basal levels of cyclic adenosine monophosphate (cAMP) or prostaglandin E1 (PGE1)-stimulated adenylyl cyclase activity (Rotrosen, Miller, and Mandio 1978; Kafka, Van Kammen, and Bunney 1979; Kafka et al. 1980; Rotrosen et al. 1980; Garver, Johnson, and Kanter 1982). Kafka, Van Kammen, and Bunney (1979) reported that basal and PGE1-stimulated cyclic AMP production were decreased in 9 schizoaffective patients (criteria not specified) as well as 11 schizophrenic patients compared to 38 normal controls. These results were still present in a somewhat larger series (Kafka and Van Kammen 1983). These investigators also found decreased adenylyl cyclase activity in platelet lysates of schizoaffective (n = 14) and schizophrenic (n = 39) patients. PGE1-stimulated adenylyl cyclase activity could be restored by the addition of guanosine triphosphate. Garver, Johnson, and Kanter (1982) also found decreased PGE1-stimulated cAMP production in eight schizoaffective patients (RDC, manic or depressed, subtype not otherwise specified) and 12 schizophrenic patients compared to normal controls. Whether these findings have any significance for the putative role of prostaglandins in schizophrenia is unknown. Regardless, they suggest a similarity between schizoaffective and schizophrenic patients.
Ventricular-Brain Ratio

Dilated cerebral ventricles were reported in a large proportion of schizophrenic patients by Johnstone et al. (1976) and Weinberger et al. (1979) on the basis of computed tomography (CT) scans. Weinberger et al. (1979) reported no difference in the ventricular size in eight patients diagnosed schizoaffective or nonschizophrenic compared to normal controls. Since then, there have been a great number of studies using quantitative CT in schizophrenics and a smaller number of studies in patients with affective disorders. Most studies have reported a much lower percentage of abnormal CT scans in schizophrenics (Andreasen et al. 1982; Jernigan et al. 1982) than originally reported by Johnstone et al. (1976) and Weinberger et al. (1979). Other studies have reported a low percentage of enlarged ventricles in patients with affective disorders which is comparable to that found in schizophrenics or normal controls (Jacoby and Levy 1980; Pearlson and Veroff 1981; Nasrallah, McCalley-Whiters, and Jacoby 1982; Kellner et al. 1983; Rieder et al. 1983; Scott et al. 1983). Rieder et al. (1983) studied 29 patients with chronic schizophrenia, 15 with chronic schizoaffective disorder, and 24 patients with major affective disorder. Diagnoses were made by RDC. There were no differences in ventricular size between any of the groups after correcting for differences in age.

We have examined the ventricular-brain ratio (VBR) in 40 schizophrenic patients; 20 with affective disorders; 11 schizoaffective, mainly schizophrenic; 5 schizoaffective, mainly affective; and 62 control subjects who had CT scans for headache evaluations that were negative for structural abnormalities (Luchins, Lewine, and Meltzer, in press). Both the schizophrenics and affective patients had significantly increased VBRs, but only 4/40 (10 percent) schizophrenics and 4/22 (18.2 percent) affective patients had VBRs greater than two standard deviations above normal. One of the 16 (6.3 percent) schizoaffective patients had a VBR greater than two standard deviations above normal. Thus, these preliminary results are in accord with the results of Rieder et al. (1982).

Differences in the methods of calculating the VBR and patient characteristics, especially age, chronicity, and perhaps some intrinsic biological characteristics such as biogenic amine abnormalities may account for the differences between studies (Luchins 1982). In any event, the available data do not permit any conclusion that schizoaffective patients are more like affective than schizophrenic patients with regard to VBR.

Neuromuscular Abnormalities

Many schizophrenic and affective psychotic patients have abnormalities of the neuromuscular system as indicated by: (1) markedly increased serum creatine kinase (CK) activity during the acutely psychotic phase of these disorders (Meltzer 1969, 1975, 1976); (2) slightly higher serum CK activity between psychotic episodes (Meltzer, Ross-Stanton, and Schlesinger 1980); (3) abnormalities of skeletal muscle fiber morphology revealed by histochemical, phase, and electron microscopic methods (Engel and Meltzer 1970; Meltzer 1972, 1973; Meltzer and Crayton 1975; Meltzer 1976); morphologic and electrophysiologic abnormalities of the subterminal motor nerve distribution (Meltzer and Crayton 1974; Crayton, Stalberg, and Hilton-Brown 1977), and a variety of abnormalities of motor nerve conduction and the Hoffmann reflex recovery curve (Goode et al. 1977; Goode, Meltzer, and Mazura 1979; Crayton, Meltzer, and Goode 1977; Metz, Goode, and Meltzer 1982). In general, there has been little quantitative and no qualitative difference between patients with affective psychoses or schizophrenia in the nature of these peripheral motor abnormalities, which may be secondary to abnormalities of the upper motor neuron influence on the lower motor neuron (Meltzer 1972). These studies invariably distinguished psychotic patients, regardless of diagnostic type, from nonpsychotic psychiatric patients and normal controls. The Hoffmann reflex recovery curve will be discussed in more detail in the next section.

The majority of these studies were carried out on patients diagnosed according to DSM-II criteria and no formal attempt to rediagnose these patients by RDC or DSM-III criteria has been made. However, the likelihood that many of the patients diagnosed as acute schizophrenia would meet RDC criteria for schizoaffective disorder, manic or depressed type, primarily affective, is very high based on our continued contact with a subgroup of these patients who have had recurrent episodes and comparison of the former criteria for acute schizophrenia and the RDC for schizoaffective illness. It is therefore not unreasonable to conclude that biochemical, morphological, and electrophysiologic abnormalities of the neuromuscular system are common to the affective, schizoaffective, and schizophrenic psychoses as diagnosed by RDC. Nevertheless, specific prospective studies of schizoaffective patients would be of interest to demonstrate this point unequivocally.
H-Reflex

The recovery curve of the Hoffmann reflex measures the excitability of the spinal α-motoneuron pool. It has been reported to be abnormal in psychiatric patients in several studies from this laboratory (Crayton, Meltzer, and Goode 1977; Goode et al. 1977; Goode, Meltzer, and Mazura 1979; Metz, Goode, and Meltzer 1980; Metz, Holcomb, and Meltzer 1982). In the only study which specifically examined the recovery curve in unmedicated patients diagnosed according to RDC (Metz, Goode, and Meltzer 1980; Metz, Holcomb, and Meltzer 1982), 17 schizoaffective patients were compared to 30 schizophrenic, 17 manic, 17 depressed, 9 other psychotic, and 61 normal subjects. The recovery curve in all patient groups was found to be higher than that of normals. The incidence of abnormalities outside the range found in the normal subjects was 27 percent among the schizophrenics, 24 percent among the schizoaffectives, 15 percent among the affectives, and 22 percent among the "others." Depressed patients showed a higher incidence of abnormalities than manic patients, both within the schizoaffective group (27 vs. 17 percent) and within the affective group (24 vs. 6 percent). Thus, schizoaffective depressed and depressed patients were more like the schizophrenics than the manic patients.

In another study (Metz, Holcomb, and Meltzer, in preparation), 14 RDC affective patients and 9 schizoaffective patients were studied before and after receiving 200 mg of 5-hydroxytryptophan (5-HP) orally. Five of the nine schizoaffectives (56 percent) had lower recovery curves after 5-HP, in contrast to only 2/14 (29 percent) of the affective patients, and 15/18 (83 percent) of the normals. There are no data yet for schizophrenic patients.

Sleep Studies

It has long been recognized that sleep disturbances are characteristic of major depression. Most depressed patients show changes in sleep continuity and inability to remain asleep. Decreased overall sleep time is very common as is reduced delta sleep (slow wave sleep, stages 3 and 4). These changes are nonspecific since they are present in other neuropsychiatric and medical disease states, especially those with a chronic course (Kupfer and Foster 1975). The latency of rapid eye movement (REM) sleep—the interval from the onset of sleep until the onset of the first REM period—and increased eye movement density during the first REM period are highly sensitive and specific markers for unipolar and bipolar primary depression (Kupfer 1976; Gillin et al. 1979). Thus, the mean REM latency in a group of 47 primary depressives was 38.6 ± 3.2 minutes compared to 72.3 ± 4.3 minutes in 48 cases of secondary depression. In general, schizoaffective patients display the same abnormalities.

Kupfer’s group (Kupfer and Foster 1975; Reich et al. 1975; Kupfer et al. 1979) has compared the sleep of schizoaffective depression to schizoaffective depression and primary depression. Six schizoaffective depressed patients were differentiated from acute and latent schizophrenics by shortened REM latency and increased REM activity (Reich et al. 1975). The REM latency of the schizoaffective group was approximately 32 minutes compared to 81 and 98 minutes for the acute and latent schizophrenics, respectively. In a second report, they noted no difference between the sleep of these six schizoaffective patients and that of nine psychotic depressed patients (Kupfer and Foster 1975). More recently, Kupfer et al. (1979) reported on 12 patients with schizoaffective depression (RDC criteria, subtype not specified) and 29 psychotic depressed patients. A major sleep continuity disturbance as shown by sleep onset difficulty of over 1 hour, increased early morning awakening of over 30 minutes, and low overall sleep efficiency was present in both groups. Increased stage 1 and decreased stages 3 and 4 were present. The REM latency was short (41 ± 33 minutes) in psychotic depression and in schizoaffective patients (43 ± 28 minutes). No significant differences in measures of sleep continuity, sleep architecture, or REM sleep were present in the two groups with the exception of a slightly shortened first REM period in the schizoaffective depressed group. A longitudinal study of 5 RDC schizoaffective depressives, 5 primary psychotic depressives, and 12 nonpsychotic depressives found the distribution of REM latencies to be similar in all groups (Coble, Kupfer, and Shaw 1981). Another study (Benson, Berger, and Zarcone 1980), also using RDC, studied nine schizoaffective patients and found no differences between the schizoaffective patients and six patients with major depression. The schizoaffective patients did differ from normals (n = 19) on several parameters and from schizophrenics (n = 9) on percent stage 4 and percent REM, with the schizoaffectives being lower on both of these measures.

In a study of the phasic activity in REM, Benson and Zarcone (1982) studied 12 normal, 11 schizophrenic, 8 schizoaffective, and 10 depressed males (RDC). They examined middle ear muscle activity (MEMA) and reported that the schizophrenics were
significantly higher than all other groups, but the schizoaffective were significantly lower than either the normal or the depressed group. Among the schizophrenics there was no relationship between MEMA rate and eye movement rate, so MEMA, which appears to distinguish schizoaffectives from both schizophrenics and depressed patients, is probably an understudied variable, not the equivalent of eye movement density.

Thus, although some sleep parameters strongly suggest schizoaffective depression is a variant of primary depression, another sleep parameter (MEMA) indicates the schizoaffective patients differ from both major affective and schizophrenic patients. It would be of interest to study MEMA and REM latency and density in a large cohort of schizoaffective, schizophrenic, and major depressed patients.

**Eye Tracking**

Holzman et al. (1974) reported that schizophrenic patients had a high incidence of smooth pursuit eye-tracking abnormalities. This study included six patients diagnosed as schizoaffective, the criteria including significant schizophrenic symptomatology with clear affective components. Fifty percent of the schizoaffective patients were deviant on a pendulum tracking task, compared to 86 percent of the chronic schizophrenic patients (n = 29), 22 percent of the manic-depressive patients (n = 9), 20 percent of the nonpsychotic patients (n = 19), and 8 percent of the normal subjects (n = 72). However, the schizoaffective patients had fewer velocity arrests than any group, including the normals. Shagass, Amadeo, and Overton (1974) compared eye tracking in age-matched normal subjects to that in schizoaffective (n = 7), schizophrenic (undiifferentiated, n = 16); paranoid (n = 6); latent (n = 6); depressed (n = 6); schizoaffective depressed (n = 10); manic (n = 5); nonpsychotic (n = 12); and alcoholic (n = 7) patients. The schizoaffective patients were the only psychotic patient group which did not differ from the controls on measures of velocity arrest. A subsequent study (Klein et al. 1976) failed to find a difference between schizophrenic and nonschizophrenic patients, although both groups differed from normals. The authors speculated that their failure to find a diagnostic differentiation among the patients may have been due to the inclusion of 9 schizoaffective patients among their schizophrenic group (total n = 10). All of these studies were completed before the introduction of the RDC. Other than the study of Klein et al. (1976), they suggest schizoaffective patients may be less abnormal than schizophrenic or even affective patients with regard to velocity arrests, although other parameters are intermediate in incidence of abnormality. In reviewing this literature, Spohn and Larsen (1983) note the high probability that eye tracking dysfunction is common to the functional psychoses. They advocate the study of eye tracking in schizoaffective patients, separating those with genetic loading of schizophrenia from those with a genetic loading of affective disorder to determine if eye tracking could be a genetic marker.

**Electroencephalogram (EEG) and Evoked Potentials**

The literature relating EEG and evoked potentials to various forms of psychosis has been reviewed by Shagass (1975). Several measures were indicated as having the possibility of distinguishing schizophrenia and affective psychoses. Since 1975, other studies of the EEG have demonstrated the capacity to make the schizophrenic-affective differentiation (Abrams and Taylor 1979; Shagass, Roemer, and Straumanis 1982). Similarly, evoked potential paradigms in the somatosensory (Shagass et al. 1980) and auditory modalities (Roth et al. 1981) have distinguished schizophrenic from depressed patients. The performance of schizoaffective patients on these paradigms has not yet been reported.

**Conclusions**

The studies we have reviewed are clearly preliminary in nature. Given the need to subdivide schizoaffective patients into at least the four, or possibly six, categories of the RDC, depending upon whether those patients who fit both mainly affective and mainly schizophrenic subtypes are included with the mainly affective or mainly schizophrenic subtypes, it is rare for studies to include an adequate number of each major subtype. Although we favor the RDC system for diagnosis in studies of schizoaffective illness, it is not possible to be confident that the RDC best identifies the group of patients that should be considered in the schizoaffective category. Ideally, biological studies would use multiple criteria sets to distinguish schizoaffective from affective and schizophrenic patients in order to determine whether or how changes in criteria affect the ability of biological measures to clarify the relationships between the syndromes.

The biological evidence we have reviewed suggests significant overlap between the schizoaffective disorders and the affective disorders. Thus, both groups, but not schizophrenics, show abnormalities in platelet 5-HT uptake, CSF tryptophan, TRH-
induced increase in TSH, REM latency and REM density, and absence of exaggerated increases in growth hormone following apomorphine. The sleep and platelet 5-HT uptake studies appear to be the most convincing of this category. However, there is a cluster of studies which show greater similarity between schizoaffective patients and schizophrenics than between schizo-affective and affective patients: CSF NE, clonidine-induced decrease in plasma MHPG, platelet 5-HT content, and PGE₂-stimulated adenylate cyclase activity. Other studies show abnormalities common to all three groups of psychoses: blunted dexamethasone suppression, low MHPG and eye tracking abnormalities (schizoaffectives intermediate in frequency between schizophrenia and affective disorders), elevated CSF GABA, and neuromuscular abnormalities such as increased plasma CK activity. There are also some studies showing unique abnormalities in the schizoaffective patients, e.g., platelet α₂-adrenergic receptor number, MEMA, or abnormalities present in affective patients that are not present in schizoaffective disorder, e.g., elevated plasma NE.

This varied group of results, if confirmed by further investigation, would not support the simple model that all schizoaffective disorders are a phenocopy of the affective disorders. It would be more supportive of the hypothesis that some cases of schizo-affective disorder are phenocopies of affective disorder and some of schizophrenia. However, it is also consistent with a continuum model of psychosis. This could be based on a polygenic model in which patients with the major psychoses share a number of genetic influences in common.

References


Brockington, I.; Crow, T.J.; Johnstone, E.C.; and Owen, F. An investigation of platelet monoamine oxidase activity in schizophrenia and schizo-affective psychoses.


Gillin, J.C.; Duncan, W.; Pettigrew, K.D.; Frankel, B.L.; and Snyder, F. Successful separation of depressed, normal and insomniac patients by EEG sleep data. Archives of General Psychiatry, 36:85-90, 1979.


Lake, C.R.; Ziegler, M.G.; Van Kammen, D.P.; and Murphy, D.L. "Can Plasma Norepinephrine Levels Differentiate Schizophrenia From Major Affective Disorders?" Presented at the Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, December 1982b.


Prange, A.J., Jr.; Loosen, P.T.; Wilson, I.C.; Meltzer, H.Y.; and


Shagass, C.; Roemer, R.A.; Straumanis, J.J.; and Amadeo, M. Topography of sensory evoked


Tyrrell, D.A.J.; Parry, R.P.; Crow, T.J.; Johnstone, E.C.; and Ferrier, N.


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