Vulnerability and Schizoaffective Psychosis: A Two-Factor Model

by William Braden

Abstract

Remitting illness such as affective or schizoaffective disorder is appropriately described by a vulnerability model. Clinical evidence is reviewed here to clarify the relationship between the affective-disorder-like and schizophrenia-like symptoms in a schizoaffective episode. A model is proposed which treats vulnerability to schizoaffective and schizophreniform psychosis as the result of two factors. The first factor is vulnerability to an episode of psychotic illness characterized by psychomotor and vegetative activation. The second is vulnerability to cognitive disturbance in response to increased activation. The relationship between stress and increased activation may be mediated by dopaminergic systems; this relationship is probably specific neither to etiology nor to diagnosis. The relationship of cognitive symptoms to episodes of activation is unclear. The model presented here may help organize and interpret research in this area, especially as traditional research designs which emphasize comparisons between diagnostic groups may not address these questions adequately.

Models of the etiology of the major psychoses have become increasingly complex. Rosenthal (1970) described several models of schizophrenic etiology: the relatively simple monogenic-biochemical and life-experience models, and a diathesis-stress model. The diathesis-stress model postulates an inherited “constitutional predisposition” to schizophrenia. Environmental stresses interact with the predisposition in such a way as eventually to produce overt illness. Zubin and Spring (1977) proposed a vulnerability model that differs in important respects from the diathesis-stress model. Vulnerability is seen as a relatively enduring trait that predisposes to psychosis, but it includes both genetic and acquired components such as perinatal complications and family experiences. Thus, some of the developmental events included in the “stress” component of the diathesis-stress model are included in the “vulnerability” component of the vulnerability-stress model. Vulnerability is a phenotypic trait that Zubin and Spring hope can be measured.

Another difference is that stressors or “challengers” are seen as provoking episodes of illness, rather than an entire illness. Zubin and Spring view schizophrenia largely as an episodic or remitting illness. Although hospitalizations of schizophrenic patients nowadays are more likely to follow an episodic pattern, many schizophrenics between episodes suffer from deficits in social, cognitive, and affective functioning, and from active symptoms such as auditory hallucinations. Therefore, if a vulnerability model is appropriate to episodic illness, perhaps it could help us understand affective and schizoaffective illness as well as, or better than, schizophrenia.

As Strauss and Carpenter (1975) have pointed out, the correspondence between the different dimensions of a psychotic illness—symptoms, course, and social functioning—is quite imperfect, raising the possibility that different models will be appropriate to each dimension. Thus, a vulnerability model might fit the acute episodes, while another type of model might better describe the symptoms and deficits between episodes.

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I present here a vulnerability model of schizoaffective psychosis which (1) examines the relationship of the "schizophrenic" and "affective" components of the acute episode, and (2) describes a more general vulnerability model for organizing research on the major psychoses.

Thought Disorder and Mood Disorder: A Starting Point

Although the advent of DSM-III (American Psychiatric Association 1980) has changed the basis of diagnostic classification in the major psychoses, some older theoretical assumptions tend to persist, namely, that manic-depressive illness (MDI) is a disorder of mood, while schizophrenia is a disorder of thinking or psychological function. The names "schizophrenia" and "affective" disorder embody these assumptions to some degree, and there is evidence that clinicians still think in these terms when making diagnoses (Lipkowitz and Idupuganti 1981). The existence of schizoaffective episodes, regardless of how they are classified, is not compatible with the conceptualization of the major psychotic disorders as two separate processes, one of psychological disruption, and the other of mood dysregulation. (The term "schizoaffective" is used here in the older sense, to describe an acute episode with affective and schizophrenic symptoms, rather than, as in DSM-III, to indicate a condition with persistent psychotic symptoms between episodes of affective disorder.) Thus the schizoaffective episode presents a challenge to our understanding, because its manifestations include the psychomotor and vegetative changes typical of MDI and certain psychological disturbances supposedly typical of schizophrenia; the relationship between these types of symptoms remains unclear. To avoid diagnostic implications, I use the term "activated symptoms" here to refer to affective-disorder-like symptoms such as excitement and insomnia, and the term "cognitive symptoms" to refer to schizophrenia-like symptoms such as hallucinations, delusions, Schneiderian experiences, and disorganized speech and thinking.

It should be emphasized that cognitive disruption in association with excited or activated symptoms is by no means unusual (see review, Pope and Lipinski 1978). In a study using the Research Diagnostic Criteria (RDC), Harrow et al. (1982) found delusions and hallucinations in 70 percent of a manic sample, as compared to 100 percent of schizophrenics. Formal thought disorder of some degree is also common.

Andreasen (1979), using course- and symptom-related diagnostic criteria, found roughly equal amounts of thought or speech disorder rated on clinical scales, such as tangentiality and incoherence, in manics and schizophrenics. Harrow et al. (1982), using standardized tests, found thought pathology more common in manics than in schizophrenics. It is not clear to what extent the thinking disorder of manics resembles or differs from that of schizophrenics. Oltmanns (1978) found similar distractibility during a learning task in both groups (RDC diagnosis).

Andreasen and Powers (1974) reported that manics were overinclusive on an object sorting task, while schizophrenics were underinclusive; Andreasen (1979) found that manics were more likely to have pressure of speech and circumsRALITY while schizophrenics had poverty of speech and poverty of content of speech. Because the schizophrenics were of established chronicity, the observed differences could have been due either to diagnosis or to phase of illness, i.e., acute versus residual.

I now consider some possible models of the abnormal processes which might generate both activated and cognitive symptoms in a schizoaffective episode, as contrasted to a classical manic episode with activated symptoms only.

Models of Cognitive Symptom Development in the Schizoaffective Episode

The word process as used here refers to a hypothetical change in brain functioning which, in theory, if not in fact, could be specified. It might consist, for example, of a change in firing rates of a group or functional ensemble of neurons. The term episode refers to the clinically observed event of an emerging illness. It corresponds to a state change, which Extein and Bowers (1979) describe as potentially reversible, typically time-limited, and once established, relatively insensitive to environmental influences. It may involve one or more pathological processes.

The following remarks apply primarily to excited episodes; their applicability to depressive episodes is discussed later.

Separate Processes Model. According to this model, fundamentally different pathophysiological processes are involved in schizoaffective episodes and affective episodes without cognitive symptoms. With the exception of the symptomatic differences in question, observations do not support the model:

• Episodes with and without cognitive symptoms may occur in the same patient (Vaillant 1963a; Ziskind, Somerfeld, and Jens 1971;
Ollerenshaw 1973; Sheldrick et al. 1977; Clayton 1982).

- Episodes with and without cognitive symptoms typically begin with apparently similar activated symptoms (Klein 1965; Carlson and Goodwin 1973; Donlon and Blacker 1973).

- Illnesses with and without cognitive symptoms occur in the same families (Vaillant 1963b; Clayton, Rodin, and Winokur 1968; Fowler et al. 1972).

- Prognosis and response to treatment with drugs or electroconvulsive therapy (ECT) is similar (Procci 1976; Pope and Lipinski 1978).

- Both types of episodes may be triggered by treatment with imipramine or similar drugs (Newman and Fisher 1964; Klein 1965).

Linked Processes Model. In this model, the basic process producing activated symptoms is the same in both types of episodes, but in some patients a second pathological process which produces cognitive symptoms is triggered by the episode.

For example, Klein and Davis (1969) hypothesized that “activation dysregulation” was common to mania and acute schizophrenia, producing similar mood and psychomotor changes; in some acute schizophrenics, however, this process induced an endogenous toxin which impaired cognition. They proposed that neuroleptics exerted their therapeutic effect by controlling the activation dysregulation. This model is more consistent with the clinical observations cited earlier than the separate processes model:

- Similar activated symptoms at the onset of the episode would be seen in both schizoaffective and affective episodes.
- Prognosis could be similar.
- Both types of episode could occur in one kindred, if it is assumed that the genes controlling the two processes are separate. The “second” gene, specifying the second process and hence the cognitive symptoms, would presumably have no effect in the absence of an episode of illness with activated symptoms.
- Treatment response could be similar, since the second, “cognitive” process is held to depend on the first, “activating” process.

However, the model does not help to explain the occurrence of both types of episode in the same individual.

A model resembling the linked processes model has been proposed by Davis (1974) for schizophrenia. He argues that the dopaminergic system, presumably the site of the therapeutic action of neuroleptics, cannot be the site of the fundamental pathology in schizophrenia, and that a second factor or process must be responsible. His primary argument is that the neuroleptics block dopamine receptors within minutes, while the process of recovery takes weeks.

Since the neuroleptics are effective in treating schizoaffective and affective episodes also (Klein and Davis 1969), Davis’s model may be relevant to the present discussion. If we assume that dopaminergic hyperfunctioning is the process that produces activated symptoms, and that a second, linked process produces cognitive symptoms, we would predict that neuroleptics would suppress activated symptoms within minutes, while cognitive symptoms might take longer to respond. Indeed, clinical observation suggests that, for some patients with acute schizophrenia, symptoms remit in just such a temporal sequence when treated with neuroleptics; that is, insomnia, hyperemotionality, and psychomotor acceleration improve before grandiosity, delusions, and hallucinations (Lehmann 1975). Whether the activated symptoms actually remit “within minutes” is a matter of disagreement. If they do not, a somewhat more elaborate model may be necessary—dopaminergic hyperactivity may not produce symptoms directly, but may be linked closely with an activated symptom process and less closely with a cognitive symptom process.

Wyatt and Torgow (1976) note that the relative therapeutic potencies of the different neuroleptics are similar in affective disorder and schizophrenia. They reject the idea that these conditions are “the same illness,” and propose instead that the neuroleptics act through a system “peripheral to the core abnormality.” Thus, the dopamine system would not be involved in pathogenesis, but might modulate motoric, affective, and cognitive activity. Klein et al. (1980) point out a third possibility, that activation disorder could be a pathological process common to both illnesses, yet due to different etiological factors. Dopaminergic involvement in symptom production may be specific neither to a single etiology (Meltzer and Stahl 1976) nor to a single diagnosis (Meltzer 1979).

Single Process Model. Although the linked model fits the data reasonably well, there is a simpler model: that both activated and cognitive symptoms are intrinsic to the same pathophysiological process. In one version of this model, differences in symptoms are related to the severity of the process; symptoms emerge in a
hierarchical fashion. Thus, mild degrees of severity are associated with changes in mood and psychomotor function; more severe illness, with disorganized thinking, delusions, and hallucinations; and extreme severity, with confusion and delirium. This model is most compatible with the *DSM-III* approach, which includes both types of episodes within affective disorder.

There are several examples of disturbances whose outward effects are primarily on mood and activity at low intensities but disrupt cognition at greater intensities. Alcohol, for example, typically produces mild euphoria and disinhibition before it produces observable changes in memory and cognitive functioning. Similar progressions have been noted with drugs whose effects are more similar to the psychotic illnesses. Post (1975) has described the effects produced by cocaine and amphetamines as a continuum of phenomena seen as the dosage or length of administration is increased: euphoria, dysphoria, and then schizophreniform states.

Likewise, the hallucinogens, while dramatically disrupting perceptual and cognitive processes at the usual experimental doses, at smaller doses produce mood fluctuations (Greiner, Burch, and Edelberg 1958). Steroid-induced psychoses may follow a similar pattern.

In fact, the underlying mechanisms of mood and cognition may both be disrupted. Mood and activity, however, normally vary somewhat and are sensitive to environmental and internal stimuli. It is more important to the organism to maintain constancy of perception and cognition; thus, there may be enough redundancy or functional reserve to allow considerable alteration to occur on the neurophysiological level before impairment is evident behaviorally.

In the naturally occurring psychoses, similar progressions have been observed by investigators of differing diagnostic and theoretical orientations. Klein (1965) described two stages of acute schizophrenia—increased affectivity and psychomotor activation, followed by the emergence of psychotic symptoms. Donlon and Blacker (1973) described the same stages in schizophrenia. Carlson and Goodwin (1973) described mania as initiated by a euphoric phase, followed by dysphoria and then overt psychosis.

Theoretically, the fact that a single drug or illness is capable of producing such a range of effects at varying dosages or over varying durations of time does not necessarily imply that a single biochemical or functional mechanism is involved. Changes in dose or duration may well invoke different processes. However, the occurrence of the same sequence of changes with stimulants, hallucinogens, and some natural psychoses strongly suggests that a hierarchical relationship can exist between activated and cognitive symptoms. Thus, if activated and cognitive symptoms occur together, we need not suppose that two separate processes were necessary to generate them.

The single process model is consistent with many of the observations that created difficulty for the multiple process models above:

- It is consistent with variation in the presence of cognitive symptoms from episode to episode in one individual, and from individual to individual within a kindred.
- It is consistent with similar response to treatment and similar prognosis whether or not cognitive symptoms are present.
- It is consistent with the appearance of activated symptoms at the onset of a typical episode.

Some predictions of this model, however, are not clearly supported. First, we would expect that cognitive symptoms would occur in only those patients with the most severe activated symptoms. We would expect to find a good correlation between the severity of activated and cognitive symptoms; however, this is difficult to assess, since overall ratings of illness severity are likely to be strongly influenced by the presence of cognitive symptoms.

Winokur, Clayton, and Reich (1969) found delusions in manics to be associated with the most severe hyperactivity. Cohen et al. (1972), however, reported affective scores of equal magnitude in schizoaffective and manic-depressive cases. Abrams and Taylor (1981) compared manics (Feighner criteria) with differing amounts of schizophrenic symptoms; they found no difference in overall severity or individual manic symptoms.

The model would be supported to some extent by indirect evidence linking the severity of the underlying illness to the presence of cognitive symptoms. For example, Mendlewicz et al. (1972) report that patients with a positive family history for MDI are more likely to have psychotic symptoms during a manic episode (although the reverse was true for depressive episodes). Gershon et al. (1982) report that schizoafffectives (RDC diagnosis) have a greater prevalence of major affective disorder in relatives than probands with affective disorder; they suggest that the schizoafffectives may have a virulent form of affective disorder. Clayton (1982) reports that excited schizoafffectives have more bipolar illness in relatives than do bipolar patients (although this was not the
and persecution for a few days after
who developed delusions of reference.

On the other hand, Fry (1978) described several bipolar patients whose manic symptoms had remitted either no drug or "antimanic agents." as they improved; treatment was through more typically manic stages psychotic manic patients passed Goodwin (1973) reported that their symptoms disappeared in the minimum length of time is required to induce cognitive symptoms, longer than the few hours of provocation obtainable with a single dose of methylphenidate. Such a delay in inducing cognitive symptoms would suggest an indirect mechanism and thus a linked process of some kind.

Third, we would expect the cognitive symptoms not only to appear last, after the activated symptoms are already present, but to disappear first as well. Unfortunately, the resolution of symptoms may be influenced by the effects of treatment. Winokur, Clayton, and Reich (1969) reported that their patients' symptoms disappeared in the following order: hallucinations, delusions, flight of ideas, distractibility, and irritability; they did not specify treatment. Carlson and Goodwin (1973) reported that their psychotic manic patients passed through more typically manic stages as they improved; treatment was either no drug or "antimanic agents." On the other hand, Fry (1978) described several bipolar patients who developed delusions of reference and persecution for a few days after their manic symptoms had remitted and before entering a depressed phase. Most, but not all of these patients, had been treated with chlorpromazine. I have observed several patients whose auditory hallucinations and ideas of reference appeared after a typical manic onset but persisted for several days after their manic symptoms had been treated successfully with neuroleptics (see also Lehmann 1975). Even if the persistence of cognitive symptoms is seen only with neuroleptic treatment, such observations would tend to support a linked model for some patients, as noted by Davis (1974). One possibility is that there are different subgroups of patients with schizoaffective symptoms, some for whom the order of resolution of symptoms is consistent with a hierarchical model, some for whom the linked model provides a better fit. Or, different models might be appropriate for different cognitive symptoms. Thus, an intrinsic or hierarchical model may be appropriate for formal thought disorder and some delusions and hallucinations, while a linked model might be more appropriate for delusions of reference and persistent auditory hallucinations.

The role of premorbid factors. Another version of the single process model relates the emergence of cognitive symptoms to the presence of preexisting factors that increase the likelihood of disorganization in the face of an activated episode (Klein 1965). These individual factors might include cognitive style, personality organization, ventricular-brain ratio, low intelligence, or specific but subclinical neurological or attentional deficits.

Prospective studies of premorbid factors comparing schizoaffective to classical manic patients are not available. Retrospective studies show that premorbid deficits in social and intellectual functioning are found more often in early-onset, unremitting schizophrenic illness than in acute or schizophreniform states (see review, Offord and Cross 1969), suggesting that obvious social or central nervous system handicaps are more closely associated with poor outcome than with acute symptomatology. In fact, excited or overactive psychotic patients are less likely than withdrawn patients to have poor premorbid histories (Depue and Dubicki 1974). In a heterogeneous sample of recently admitted, drug-free, psychotic inpatients (details in Braden et al. 1982), comparison of manics in whom psychotic symptoms were absent, mood-congruent, or mood-incongruent (DSM-III) indicated that the presence of psychotic symptoms was associated with poorer adolescent interests and sexual functioning (Braden, in preparation); however, there were no differences in duration of illness, number of hospitalizations, or ratings of chronicity of course.

For detection of more subtle handicaps, postmorbid or between-episode studies may be necessary; but such designs run the risk of confounding preexisting deficits with unknown additional deficits resulting from the episode of illness. Moreover, patients with clinically evident cognitive or functional impairment following recovery from the acute episode are likely to be excluded from samples of manic because they are rediagnosed "schizoaffective" (American Psychiatric Association 1980; Himmelhoch et al. 1981; note that "schizoaffective" refers here to a type of course or outcome, while it is used in this review to refer to a type of symptomatology evaluated at one time point). Even so, there is evidence of persisting cognitive
deficit in some, but not all, remitted manics (Asarnow and MacCrimmon 1981; Harrow et al. 1982; see also Wohlb erg and Kornetsky 1973). There is no information as to whether the patients with persistent cognitive disturbance at followup were also the most cognitively disturbed during the acute episode.

Some manic patients have been found to have enlarged ventricles, a condition which presumably persists between episodes (Pearlson and Veroff 1981; Nasrallah, McCalley-Whitters, and Jacoby 1982); again, it is not clear that the clinical presentation of this group of manics included more cognitive symptoms. There is evidence suggesting that some remitted manics have impairment of smooth pursuit eye tracking (Iacono et al. 1982) and reaction time crossover (Bohannon and Strauss, in press), measures sometimes proposed as markers of vulnerability to cognitive deficit.

Age is not a premorbid condition as usually understood, but age may modify the clinical expression of an episode. Some studies have reported earlier age of onset in schizoaffective compared to MDI patients (Cohen et al. 1972; Shopsin et al. 1976; Tsuang, Dempsey, and Rauscher 1976), while others have failed to find age differences (Abrams, Taylor, and Gaztanaga 1974; Taylor, Gaztanaga, and Abrams 1974). "Schizophrenic" symptoms are reported to occur more often in adolescent, as opposed to adult, manics (Ballenger, Reus, and Post 1982). Other interpretation of these findings is that younger patients have a more severe underlying illness, and thus are more likely to be psychotic, as specified by the hierarchical model (Taylor and Abrams 1981). Another interpretation is that younger age interacts with the illness in such a way that it predisposes to cognitive symptoms, perhaps because of incomplete biological or social maturation. This interpretation is supported by the observation that young cases with schizophrenia-like symptoms often have less cognitive disturbance in later episodes as they get older (Vaillant 1963a; Lehmann 1967; Zikind, Somerfield, and Jens 1971; Sheldrick et al. 1977; Ballenger, Reus, and Post 1982). Thus younger age may, for some patients, function as a preexisting modifying characteristic.

A combined single-process model includes both hierarchical and premorbid explanations of cognitive deficit. It specifies that the activating process has the inherent potential to disorganize or disrupt cognition, depending on severity. It also specifies that individuals do vary in their susceptibility to disorganization, as a result of preexisting characteristics of neurological organization, social adjustment, or the like. The likelihood of cognitive symptoms could be represented in crude fashion by a two-parameter model, as a function of the maximum severity of illness occurring during the episode in question, and of the threshold severity which will produce cognitive symptoms in the particular individual.

The combined single-process model will fit the observations noted above reasonably well. It could be tested in theory either by holding premorbid factors constant and looking for a correlation between episode severity and cognitive symptoms, or holding episode severity constant and looking for the correlation between premorbid factors and cognitive symptoms. In practical terms such tests will require better indicators of episode severity and more precise notions of which premorbid factors are most relevant. One problem is that affective symptoms cannot be used to measure episode severity directly, since cognitive symptoms may replace them at the height of the episode (Carlson and Goodwin 1973; Ollierenshaw 1973).

The available evidence does not allow us to choose definitively at this time between the linked and single process models. However, both the combined single process model and the linked model are vulnerability models. Vulnerability to cognitive disruption corresponds to the "second gene" in the linked model, and to premorbid factors in the combined single process model. The acute episode of activation serves as a challenge or stress which transforms the vulnerability into overt pathology.

Some observations about possible differences between manic and schizoaffective episodes do not readily fit the models above, but require other interpretations. There is some evidence that the abrupt onset of a psychotic episode is associated with more cognitive disturbance (Winokur, Clayton, and Reich 1969; Bunney et al. 1972). Faster administration of tetrahydrocannabinol has been reported to induce more psychotic thinking (Melges et al. 1974). Schizophreniform patients in one study were more likely to report precipitating events than typical affective-disorder patients (Tsuang, Dempsey, and Rauscher 1976). Postpartum manics were more likely to have Schneiderian symptoms than other female manics (Kadmas, Winokur, and Crowe 1979). These observations of the effects of abrupt onset and precipitants suggest that psychological factors can influence the individual's adaptation to an altered state: the altered, activated state can itself be viewed as an event that requires adaptive coping responses from the affected individual. Rapid onset might make
effective coping more difficult; also, coping with the altered state may be more difficult if the individual is already attempting to cope with external events.

Up to now we have been attempting to model the production of symptoms during an episode of illness. In the next section, we describe a model of the illness itself which is an extension of the model just described.

The Extended Model: A Two-Factor Vulnerability Model of Schizoaffective Illness

The extended model proposed here is also a vulnerability model. It is assumed that the disorder underlying a psychotic illness cannot be directly identified with a particular clinical state; instead, the disorder consists in a vulnerability to, or increased likelihood of, certain changes from the normal state. The current model includes two factors. First, individuals vary in their vulnerability to episodes of psychosis. Following Klein (1965), the psychotic episode is defined as a pathologically increased level of "behavioral activation," an altered state whose characteristics resemble those of the manic state. Second, individuals differ in their vulnerability to disorganization and cognitive disturbance, as described in the linked model and combined single process model above. Another implication of these models is that the two vulnerability factors are connected: an episode of illness in an individual with the first type of vulnerability is capable of inducing disorganization in individuals with the second type of vulnerability.

Vulnerability to Psychotic Episodes. The factor most readily identified as contributing to increased vulnerability to episodes of increased activation is inheritance of bipolar affective disorder. In patients with a diagnosis of bipolar affective disorder, but without a family history of illness, adverse perinatal conditions and electroencephalographic (EEG) abnormalities may also contribute to vulnerability (Dalen 1965; Hays 1976; Kadrmas and Winokur 1979).

A simple model in which risk of bipolar illness at a given time is seen as a linear combination of a constant vulnerability plus stress at the time is difficult to reconcile with findings that suggest increasing risk with increasing age or repeated illness. Early age of onset is associated with greater risk of affective illness in relatives (Mendlewicz et al. 1972; Hays 1976; Taylor and Abrams 1981); thus, increasing age may increase the risk of illness in individuals whose genetic risk is relatively low. Following an initial episode of illness, vulnerability to future episodes appears to increase: The frequency of episodes increases with repeated illness (Taschev 1974; Angst and Grof 1976; Dunner et al. 1980; Zis et al. 1980), and later episodes may be less associated with life events than the initial one (Dunner, Patrick, and Fieve 1979). It is not clear whether these effects are the result of increasing age or whether each episode increases the risk of becoming ill again (see the discussion of sensitization below).

If vulnerability is not a discrete characteristic but a continuously distributed propensity, one can imagine greater or lesser degrees of vulnerability than that represented by classical bipolar illness. On the one hand, we can conceive of individuals whose vulnerability is so high that they become ill early and in response to minimal stress. Presumably such individuals would either become continuously ill or require continuous medication to keep them asymptomatic. Clinically they might appear to be schizophrenic, although such cases have also been described as chronic mania (Van Putten and Sanders 1975). On the other hand, some individuals might have a lower degree of vulnerability, so that they enter an activated state only when unusually strong psychosocial or biological stress is present. Clinically these cases may show only sporadic or single episodes of illness, so that definitive diagnosis would be problematic; some cases diagnosed as brief reactive or postpartum psychosis might fit the model. For example, postpartum mania was found less likely to recur on followup than other mania in females; a trend toward lower incidence of family history of affective disorder was observed in the postpartum group (Kadrmas, Winokur, and Crowe 1979); these findings are consistent with the idea that postpartum cases represent a lower level of vulnerability.

Following are some specific examples of challengers that could induce or trigger an activated state. Most of the challengers listed here have been reported to produce a variety of clinical pictures ranging from manic-like states to disorganized, emotionally labile states. Some conditions that produce psychosis, such as cerebral infection, are not listed here because they may directly cause, rather than trigger, the psychosis. Thus, amphetamine is listed here, not because it causes a psychosis during the actual period of intoxication, but because it sometimes can induce a psychotic episode which lasts for days or weeks after the drug has left the body.

Drugs. Examples include: amphetamines (Bell 1965), hallucinogens
(Cohen and Ditman 1963; Bowers 1972), monoamine oxidase inhibitors (Klein 1965), tricyclic antidepressants (Klein 1965; Bunney 1978), steroids (Rome and Braceland 1952; Hall et al. 1979), phencyclidine (Allen and Young 1978), cannabis (Thacore and Shukla 1976; Treffert 1978), and levodopa (Goodwin et al. 1970). Antidepressants and levodopa may be relatively weak challengers, since virtually all reports of induction of mania or psychosis have been in patients already ill with depression, schizophrenia, or parkinsonism.

**Nondrug.** Examples include: childbirth (Brockington et al. 1981), intensive dieting with severe weight loss (Robinson and Winnik 1973), intensive psychotherapy (Glass, Kirsch, and Parris 1977), or meditation.

**Life events.** The role of life events in provoking episodes of psychosis is not clear. For bipolar illness, the proportion of episodes that follow precipitating events has been reported as 30 percent of manic episodes (Winokur, Clayton, and Reich 1969), 23 percent of episodes for early-onset and 60 percent for late-onset illness (Glassner and Haldipur 1983), and about half for initial and considerably lower for later episodes (Dunner, Patrick, and Fieve 1979). Kennedy et al. (in press) found a greater incidence of life events in manic episodes than in controls or in the same manics after discharge. It may be difficult to study the onset of mania because so many manic episodes are preceded by depressive phases lasting weeks or months (Winokur, Clayton, and Reich 1969). Also, some patients with established illness may enter a manic state following events of minimal stressfulness, such as changing to an evening shift, meeting a new boyfriend, or attending a religious retreat. Nevertheless, it is clear that a substantial proportion of episodes of MDI occur without apparent stress of either the biological or psychosocial type, suggesting the existence of as yet unidentified factors capable of inducing episodes.

Studies of life events in acute schizophrenia have been more helpful (Dohrenwend and Egri 1981). Life events were more common in the 1-year period before the onset of first-break, acute onset episodes (clinical diagnosis) than in 1-year periods in matched controls (Jacobs and Myers 1976). Life events were more likely in the 3-week period before schizophrenic onset or relapse than in the period 3 to 12 weeks before onset (Birley and Brown 1970). In this and the other British studies cited below, a symptomatic criterion of schizophrenia was used, and the samples included both chronically ill patients and patients with symptomatic recovery and retained social functioning (see, for example, Brown, Birley, and Wing 1972); hence the results are presented as relevant to schizoaffective illness.

One category of stress that does not fit a life events research strategy is chronic disturbance of familial relationships. Living with relatives who openly express hostile criticism toward the patient or who are overinvolved and intrusive (high expressed emotion or high EE) is associated with a higher rate of relapse (Brown, Birley, and Wing 1972; Vaughn and Leff 1976). Parents of adolescents who later became schizophrenic made more critical comments to them than parents of low risk adolescents (Goldstein et al. 1978), but in general the high EE factor has been studied as it affects relapse, not the onset of the original episode.

The effects of the high EE family are even stronger in those schizophrenic patients who spend more than 35 hours a week in contact with the high EE family member (Brown, Birley, and Wing 1972; Vaughn and Leff 1976). The onset of illness in patients with low EE relatives is more likely to be associated with a life event than for patients from high EE homes (Leff and Vaughn 1980); thus, onset appears to be associated either with high EE or with a life event.

The interaction of stress with neuroleptic maintenance therapy is of interest. Leff et al. (1973) reported an increased incidence of life events in the 5 weeks before relapse in patients who relapsed on drugs compared to those who stayed well on drugs; the effect was not seen in a placebo group. The investigators suggested that patients on placebo might be so vulnerable that they became ill in response to everyday interactions, while the patients on drugs were protected to some extent but relapsed with additional stress. In the family studies, 9-month relapse rates were lowered by drug treatment in the high EE group, while in the low EE group drugs did not affect the (low) rate of relapse (Brown, Birley, and Wing 1972; Vaughn and Leff 1976). At 2-year followup, more of the low EE, off drug group had relapsed, so that there was now a difference between relapse rates on and off drugs in the low EE group. It was suggested that life events may lead to relapse in the low EE group, but the rate of relapse is slower than that observed in high EE patients (Leff and Vaughn 1981).

That relatives' attitudes cause poor clinical outcome, rather than being a response to the patient's illness, is supported by two recent studies showing that therapeutic intervention with family members is effective in preventing relapse (Falloon et al. 1982; Leff et al. 1982).

Tarrer et al. (1979) reported that
schizophrenics tested in their homes had a greater rate of spontaneous fluctuations of skin conductance than controls, interpreted as evidence of higher arousal; the difference was not found with the same subjects tested in the laboratory. Entrance of a low EE relative into the room produced a lessening of the fluctuation rate, while high EE relatives did not have this effect. When subjects were tested following life events, the entrance of the relative actually increased arousal.

I have dwelt on these studies at some length because they make several important points:

- They identify at least one type of psychosocial stress capable of inducing illness that would not be detected by the usual life events approach to research or clinical history-taking.
- They clarify that most stress is nonspecific and requires a specific vulnerability to result in illness, since equally hostile and critical family members were identified for patients with depressive neurosis (Vaughn and Leff 1976). Again, of course, extraordinary stress, such as battle, may induce psychosis in patients with no other evidence of vulnerability (Dohrenwend and Egri 1981).
- Measures of autonomic arousal may help identify stressful situations, even when the correlation of arousal with clinical state is weak.
- The interactions with drug maintenance status suggest that dopamine receptor blockers can protect against the effects of stress. Thus, dopamine systems may mediate those aspects of stress response involved in the genesis of the acute psychotic episode.

Dopamine, stress, and sensitization. This last point deserves some amplification. The idea that dopamine systems may mediate some aspects of psychosocial causation of psychosis is hardly novel (Pollin 1972). Post (1975) pointed out similarities between the effects of stress and stimulant drugs, citing evidence that acute stress leads to catecholamine discharge, while chronic stress may deplete catecholamines. In rats, physical stress such as tail pinch induces eating, aggressive, or copulatory behavior that depends on dopaminergic neurons (Antelman and Szechtman 1975); similar effects can be produced by amphetamines alone (Antelman et al. 1980).

There is evidence that in dopamine systems a type of learning called "sensitization" occurs, in which repeated stimulation causes the system to become more responsive to stimulation. Chronic amphetamine administration can sensitize to the effects of amphetamine in producing stereotypy in animals and dyskinesia in humans (Klawans and Margolin 1975; Segal and Janowsky 1978; Antelman et al. 1980). Clinically, sensitization to amphetamine psychosis in humans occurs as well (Klawans and Margolin 1975; Segal and Janowsky 1978).

In rats, there is cross-sensitization between amphetamine and physical stress: repeated stress sensitizes to amphetamine, and repeated amphetamine administration sensitizes to physical stress (Antelman et al. 1980). In humans, repeated use of amphetamines not only sensitizes to amphetamine psychosis as already noted, but to the development of nondrug-induced psychotic episodes as well (Breakey et al. 1974; Utena 1974; McLellan, Woody, and O'Brien 1979).

To round out this picture completely, we would predict that in some individuals, chronic or repeated stress would not only induce episodes in vulnerable individuals, but increase vulnerability as well. Thus, vulnerability would have a developmental aspect, rather than remaining completely static; this is consistent with the observation that relapses are precipitated by less severe stressors than those that triggered the onset of the initial episode (Wynne 1978).

Finally, it should be emphasized that even if the dopamine system does indeed mediate the relationship between stress and activated or psychotic behavioral changes, the etiology or "lesion" in a given illness need not be in the dopamine system. It could just as well be in other systems that regulate or modulate the activity of the dopamine system, such as the norepinephrine or serotonin systems (Antelman and Caggiula 1977), and several types of etiologies are consistent with such a model (Melzer and Stahl 1976).

Improving the Definition of the Activated State

The analysis presented above separated the clinical manifestations of the schizoaffective episode into activated and cognitive components. The empirical usefulness of the models presented will require better operational definition of these components.

Klein (1965) suggested that the psychomotor and affective symptoms of mania and acute schizophrenia are due to "activation dysregulation" involving centers controlling arousal, pleasure, pain, emotionality, and activity level. While such hypotheses may prove to be entirely accurate, they have been difficult to test directly. Without attempting to specify the pathological processes in neurophysiological or biochemical terms, it would be useful to have
clinical and/or laboratory markers for the episode of activated symptoms. This would allow:

• Comparisons, among patients with activated symptoms, between those with greater and those with lesser cognitive symptomatology.
• Comparisons, among cognitively disturbed patients, between those with and without activated symptoms, to determine whether certain types of cognitive dysfunctions are associated with the activated state.
• Longitudinal comparisons of cognitive dysfunction during and between activated episodes.

Clinically, the prototype of the activated state is the manic syndrome. The traditional hallmark of this state is the characteristic mood disturbance of euphoria or expansive mood (modified in DSM-III to include irritability). In many schizoaffective episodes, however, a predominant mood is hard to define. Mixed episodes, with manic and depressive affect alternating or intermingled, are not uncommon, occurring in 10–25 percent of patients with MDI (Winokur, Clayton, and Reich 1969; Himmelhoch et al. 1976). Mixed or dysphoric presentations may be especially common in psychotic patients (Court 1968; Carlson and Goodwin 1973; Ollendick 1973). Possibly increased emotionality would serve better as a clinical marker of the activated episode. Decreased sleep is not specific to episodes of affective or psychotic illness, but it may be useful to exclude patients with undisturbed sleep from a study of activated patients. Increased activity, whether physical or verbal, can be readily observed and measured (Venables 1957).

These clinical indicators have severe limitations. Thus, if we are confined to a clinical definition of activation, about all we can do with these tools is to state whether a particular acute episode is of the activated type or not. We cannot investigate, for example, whether a chronic activated state has different manifestations. We cannot measure the severity of activation throughout its range, because some of the most severe episodes may be associated with atypical, even paradoxical, features such as loss of affect and catatonic symptoms. Without other indicators we have no means of resolving these issues.

Laboratory markers of the activated state would thus be desirable. Activation is probably not identical with arousal. Findings of increased autonomic and EEG arousal are most marked in chronic schizophrenic patients; certainly there is no convincing evidence of increased arousal in acute psychosis (Lader 1975; Neale and Oltmanns 1980). Indeed, using Venables' (1957) activity-withdrawal measure, there is evidence that “active schizophrenics” (most of whom would receive RDC diagnoses of mania or schizoaffective disorder; Klein 1982) are underaroused (Depue and Fowles 1974), while the highest levels of autonomic arousal are found in withdrawn schizophrenics (Venables and Wing 1962).

Serum creatine phosphokinase (CPK) is typically elevated in acute psychotic illness. The finding is diagnostically nonspecific, as it occurs in schizophrenia and affective illness alike, as well as some organic brain diseases. It is strongly associated with recent onset of the episode, and also, less strongly, with hyperactivity, anger, paranoia, and psychotic behavior (Meltzer 1976). CPK may thus be a better marker for the onset of an episode than for its continuous presence. Murray et al. (1979) report increased excretion of dimethyltryptamine (DMT) in paranoid schizophrenics, manics, and “other” psychotics (Catego diagnosis); DMT excretion appears to return to normal with clinical improvement.

If cognitive disturbances are an integral part of the pathophysiology of MDI, as implied by the single-process model, then it might in the future be possible to establish certain cognitive function tests as markers of the activated episode. I will speculate briefly on what some of these might be.

One clinical feature of excited episodes is rapid shifting of attentional focus and mental content, reported subjectively as “racing thoughts” (Braden and Ho 1981) and observed as flight of ideas, tangentiality, and incoherence (Andreasen 1979). As noted by Fischer (1971), the increased rate of shift in mental content is consistent with an aroused, creative state, but at greater severity can appear as a schizophreniform state, when the flow of data outstrips the individual’s ability to process it adequately. Related tests might include overinclusiveness (Andreasen and Powers 1974), or possibly divergent production (e.g., “How many names of places can you think of in a minute?”). Manics have longer simple reaction times during the episode (Court 1968), and may perform better at fast rates of motor response (Stein 1977). Underproduction of time intervals (corresponding to overestimation of measured intervals) has been noted in psychotics, especially acute schizophrenics (Melges and Fougerousse 1966).

Another clinical feature is heightened sensory perception, which may correspond to laboratory
findings of better than normal resolution, in acute psychotics, of visual flicker (McDonough 1960; Johanssen, Friedman, and Liccione 1964), and auditory double pulses (Collins et al. 1978).

Stable configurations of perceptual or response tendencies presumably require inhibitory processes, which may be weakened or impaired in manic states. Detailed models have been proposed for schizophrenic episodes (Venables 1964; Joseph, Frith, and Waddington 1979). Possibly an evoked response measure could be found which would reflect such changes. (For more general surveys of potential markers, see Zubin and Steinhauer 1981; Buchsbaum and Haier 1983).

Other Conditions: Depression and Schizophrenia
The discussion so far has dealt with excited episodes. It is possible that some depressive episodes may meet the definitions of activated state proposed here. For example, some agitated depressions show overactivity, increased emotionality, and insomnia; these conditions are more likely than other depressive states to respond to treatment with neuroleptics (Hollister et al. 1967). Other depressive states, such as hypersomnic, anergic states, may involve quite different processes.

The entire group of depressive conditions, however, is probably milder and more heterogeneous than manic or schizoaffective states. Hospitalized depressives, like manics, show cognitive deficits on formal testing (Miller 1975; Raskin, Friedman, and DiMascio 1982). However, depressive patients with delusions and hallucinations appear to differ from other depressives in treatment response (Charney and Nelson 1981) and outcome (Coryell, Tsueng, and McDaniel 1982); they are more likely than other depressives to have enlarged ventricles (Targum et al. 1983). Thus, one can distinguish psychotic from nonpsychotic patients more readily in depression than in mania. It will be of interest to compare functional and biological characteristics of manic and depressive schizoaffective patients, especially with the subgroup of depressives who manifest hyperactivity and overemotionality.

The model of psychosis presented here is a phasic one. Crow (1980) has recently proposed a phasic model of schizophrenia, in which the acute schizophrenic phase or type I syndrome is associated with changes in dopaminergic transmission. It would be of interest to determine to what extent the activated phase that characterizes schizoaffective or manic episodes resembles the acute phase of chronic schizophrenia.

Conclusions
1. If schizoaffective states indeed represent a type of affective disorder, it may be useful to inquire how the appearance of cognitive symptoms relates to the pathophysiology of the affective symptoms. The activated or excited state appears to be closely associated with the cognitive symptoms, although the exact mechanism is not clear. The occurrence of the activated state fits a vulnerability model.

2. The activated state may be diagnostically and etiologically nonspecific. However, its clinical expression may be related to dopaminergic activity, since neuroleptics suppress it, and it can be mimicked or induced by dopamine agonists. Of particular interest is the idea that dopaminergic systems may also mediate psychotic reactions in response to life stress. Vulnerability may increase with time as sensitization occurs in the dopaminergic system or related systems.

3. The activated state may be inherently disruptive to cognition, although a requirement for additional mechanisms cannot be ruled out. Cognitive symptoms depend on the level of activation, and also on preexisting central nervous system (CNS) deficits (also diagnostically nonspecific). In the remitting psychoses, CNS deficits between episodes may be subclinical but make the individual vulnerable to cognitive disturbance during episodes.

4. Presumably there exist specific illnesses and etiological mechanisms which can produce psychosis; at present, however, we cannot identify them with any certainty. In the absence of such identification, the understanding of cognitive disturbance in the major psychoses will require research designs which relate specific cognitive symptoms to specific clinical features such as premorbid status or the presence or absence of excitement (even when such features are not diagnosis-specific). Longitudinal designs which examine cognitive deficits both during and between acute episodes will be important as well. Research designs based on diagnostic classification alone cannot deal with such questions effectively.

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