

The Two-Syndrome Concept: Origins and Current Status

by Timothy J. Crow

Abstract

The two-syndrome concept postulates two "dimensions of pathology" underlying schizophrenia—a reversible (and potentially neuroleptic-responsive) component and a sometimes progressive and relatively irreversible component associated with the deficit state and poor long-term outcome. Negative symptoms (narrowly defined) appear to be more closely associated with the latter component (the type II syndrome), as also are cognitive impairments, abnormal involuntary movements, and behavioral deterioration. This syndrome is assumed to be more closely related than the type I syndrome of positive symptoms to the structural brain changes inferred from pneumoencephalograms, computed tomography scans, and recent post-mortem studies. However, since both syndromes often occur in the same patient—sometimes at the same point in time—they presumably have the same etiology.

Whether the celebrated razor is that "entities are not to be multiplied without necessity" or, as Bertrand Russell (1946) suggests William of Occam actually wrote, that "It is vain to do with more what can be done with fewer," the principle is surely profound. Explanatory concepts must be simple and as few as can be.

Since Kraepelin (1919), the simplest view of schizophrenia is that it is a single disease with a single pathology. With respect to etiology (when the relatively rare schizophrenia-like psychoses of amphetamine intoxication and temporal lobe epilepsy are excluded), there is as yet little reason to doubt he was right. Dr. Sommers, in her contribution to this issue, misquotes me as suggesting the two symptom

classes characterize etiologically distinct schizophrenic subtypes. I do not believe I can be misunderstood as having said this. Indeed, I believe a simpler view (i.e., that manic-depressive psychosis and schizophrenia have the same basic etiology; Crow 1984) is still tenable. It may turn out not to be so, and schizophrenia may eventually be shown to have many etiologies, as Bleuler (1950) implied, but until one etiology is established and this etiology is shown to be absent in some cases, Occam's razor should be applied.

For the same reasons, the view that more than one "dimension of pathology" underlies the manifestations of schizophrenia (Crow 1980; Crow et al. 1982) requires a defense. The concept that two pathological processes are present and that these can be related to particular constellations of symptoms arose from three studies conducted in the Division of Psychiatry at Northwick Park between its inception in 1974 and 1978:

1. The first computed tomographic (CT) study in schizophrenia (Johnstone et al. 1976, 1978b) demonstrated that cerebral ventricular area in a group of chronic institutionalized patients was significantly greater than that in a group of age- and premorbid occupation-matched controls. Ventricular enlargement could not be explained by previous physical treatments, and within the schizophrenic group was correlated (significantly) with cognitive impairment and (nonsignificantly) with the presence of negative symptoms.

2. A study of the therapeutic effects of the two isomers of the

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thioxanthene flupenthixol (Johnstone et al. 1978a) tested the dopamine blockade hypothesis of the antipsychotic effect (B-flupenthixol being more than 1,000 times less potent than the *a*-isomer as a dopamine antagonist). In recently admitted patients with acute episodes of schizophrenia, the *a*-isomer was significantly more active than the B-isomer, which itself was no more effective than placebo. In these patients negative symptoms (flattening of affect and poverty of speech) were relatively infrequent and seldom severe, but when present showed little tendency to improve on placebo and no differential response to dopamine receptor blockade.

3. In a post-mortem study (Owen et al. 1978), dopamine turnover (assessed by homovanillic acid or dihydroxyphenylacetic acid concentrations) was not increased but numbers of D₂ dopamine receptors (assessed as ³H-spiperone binding) were increased. Although the question of whether this change is related to the disease process rather than to neuroleptic drugs is not yet resolved (see, for example, Mackay et al. 1982; Crow et al. 1984), in later work (Crow et al. 1981b) the number of D₂ receptors in post-mortem brain was found significantly related to positive, but not negative, symptoms assessed in life.

Together these observations presented a crisis of interpretation. If schizophrenia was a unitary disease process, was this to be seen as a primarily neurochemical disturbance (as suggested by the dopamine hypothesis and the responsiveness of at least some schizophrenic symptoms to neuroleptic drugs)? Or as a destructive process leading to structural brain changes and intellectual impairment as the results of the CT scan study and some earlier pneumoencephalographic

studies (e.g., Huber 1957; Haug 1962; Asano 1967) might lead one to suspect? The dopamine hypothesis had its attractions (in my view, it is the only neurochemical theory that is still viable), but it could not explain the intellectual impairments or why some patients do badly in spite of neuroleptic medication. Nor could the less popular view that schizophrenia is a low-grade early onset form of dementia explain the not infrequent, apparently complete recoveries after individual episodes of illness, the effectiveness of neuroleptic medication, or the ability of amphetamine-like compounds to provoke delusions and hallucinations closely resembling those seen in idiopathic schizophrenia.

For these reasons, when reviewing the neurochemistry of schizophrenia, I outlined the difficulties for the unitary viewpoint and suggested the recent findings could only be accommodated if one assumed that more than one "dimension of pathology" was present (Crow 1980). Specifically, I suggested there was a neurochemical component (perhaps related to dopaminergic transmission) responsive to neuroleptic medication, and a structural component related to poor long-term outcome and to the intellectual impairment that undoubtedly sometimes occurs. With the results of the flupenthixol isomers trial (Johnstone et al. 1978a) in mind, I suggested the drug-responsive component could be related to positive symptoms. On the basis of the CT scan study (Johnstone et al. 1976, 1978b) and other data showing a relationship between negative symptoms and intellectual impairment (Owens and Johnstone 1980), I proposed that the negative symptoms, which in the flupenthixol isomers study had appeared resistant to neuroleptic medication, were more closely related to poor long-term

outcome, and that this component (i.e., negative symptoms and intellectual impairment) was associated with structural changes in the brain. Thus, the paradox that the symptoms of the disease sometimes remit and more often respond to neuroleptic drugs, but at the same time the disease not infrequently has a poor long-term outcome unresponsive to drugs, could be resolved on the basis that there are potentially reversible (perhaps dopamine-related) and irreversible components. (See table 1.)

An important aspect of this hypothesis is that it attempts to relate the two postulated pathological processes to clinical manifestations. I see now (and the diverse contributions to this issue amply demonstrate the point) that the definition of positive and negative symptoms is crucial to whether one regards this aspect of the concept as having content. In brief, it is essential that one adopt a narrow definition of negative symptoms. In the Northwick Park studies, we had two advantages: (1) Before it was published, David Goldberg drew my attention to the schizophrenia rating scale (Krawiecka, Goldberg, and Vaughan 1977), which he and the late Maria Krawiecka had devised. It is simple to use, has explicit operational rules, and focuses on eight key areas: delusions, hallucinations, thought disorder (incoherence of speech), flattening or incongruity of affect, poverty of speech, retardation, depression, and anxiety. We used this scale in all our early work and indeed still find it useful and practical. (2) Eve Johnstone early concluded that flattening and incongruity of affect could and should be rated separately. When this is done, there are nine items in the scale. Of these, three (depression, anxiety, and

Table 1. Two syndromes in schizophrenia¹

	Type I	Type II
Characteristic symptoms	Hallucinations, delusions, thought disorder (positive symptoms)	Affective flattening, poverty of speech, loss of drive (negative symptoms)
Type of illness in which most commonly seen	Acute schizophrenia	Chronic schizophrenia, the "defect" state
Response to neuroleptics	Good	Poor
Outcome	Reversible	Irreversible?
Intellectual impairment	Absent	Sometimes present
Postulated pathological process	Increased dopamine receptors	Cell loss and structural changes in the brain

¹ Reprinted, with permission, from Crow (1980).

retardation) are nonspecific; two (delusions and hallucinations) are clearly positive symptoms; two more (thought disorder and incongruity of affect) may be so considered, although the decision is less obvious; and two (flattening of affect and poverty of speech) are clearly negative.

Origins of the Positive and Negative Symptom Terminology

Berrios (1985) has traced the historical origins of the positive-negative symptom terminology in the neurological literature. He attributes its introduction to Reynolds (1858), and he is surely right to assert that the implications that Hughlings Jackson attributed to the distinction (viz. that positive symptoms are secondary "release" phenomena, which result from the destruction of tissue, which leads directly to the negative symptoms) are inappro-

priate to the psychiatric literature. Hughlings Jackson is an esteemed authority but irrelevant to recent discussions of schizophrenia. A loose adherence to his views has been the source of confusion, particularly insofar as some have been tempted to equate Bleuler's "fundamental" symptoms, from which he thought the "accessory" symptoms were derived, with negative symptoms.

Berrios attributes the introduction to the psychiatric literature of the concept of positive and negative symptoms as independent phenomena to de Clérambault (1942). Andreasen (this volume) refers to Fish's (1962) book on schizophrenia as one of its recent sources, but I have been unable to identify a point in that book (except in relation to thought disorder, p. 25) where Fish discusses the issue in a way which gives any indication that he regarded it as significant. On the other hand, the terminology has been used quite widely in the United Kingdom—for example, by J.L.T. Birley, J.K. Wing,

and their collaborators (see, for example, Wing and Brown 1970, pp. 18–19; Wing 1978). Wing (1978) contrasts "florid or positive or productive" symptoms seen particularly in acute episodes with the negative components of the clinical "poverty syndrome," which he identifies as "emotional apathy, slowness of thought and movement, underactivity, lack of drive, poverty of speech and social withdrawal" (pp. 4–5). He considers that there are three basic groupings—the positive syndrome of acute schizophrenia, the negative (or clinical poverty) syndrome of chronic schizophrenia, and combinations of the two. This is roughly the concept we adopted at Northwick Park, although by the use of the Krawiecka scale we have defined negative symptoms more narrowly, and would regard certain of the symptoms that Wing lists (e.g., underactivity and social withdrawal) as less specific and in some circumstances secondary to positive symptoms. Wing also

considers the tripartite scheme (i.e., positive symptoms, negative symptoms, and both together) an oversimplification and, for example, draws attention to the frequency of thought disorder as a component of the chronic syndrome.

Another line of thought regarding positive and negative symptoms and their interrelationships was followed by Strauss, Carpenter, and Bartko (1974). These authors quote Kraepelin in support of the single process concept:

We are justified in regarding the majority at least of the clinical pictures which are brought together here as an expression of a single morbid process, though outwardly they often diverge very far from one another [Kraepelin 1919, p. 3]

and contrast this concept with the title of Bleuler's book *Dementia Praecox, or The Group of Schizophrenias*. Strauss, Carpenter, and Bartko (1974) trace their use of the positive-negative terminology back to Hughlings Jackson, but they do not adopt his inference of a causal sequence between them. They include as positive symptoms "disorders of content of thought and perception, certain types of form of thought (e.g., distractibility), and certain behaviors (e.g., catatonic motor disorders)," (p. 65) and as negative symptoms "blunting of affect, apathy, and certain kinds of formal thought disorder, such as blocking" (p. 65). This last inclusion is somewhat surprising, as also is these authors' insistence that "disorders of relating" constitute a third dimension that has to be considered quite separate from both positive and negative symptom components (p. 65).

Strauss, Carpenter, and Bartko (1974) conclude regarding their three groups of symptoms that:

1. Positive symptoms can develop or resolve over a relatively short period of time. Sometimes they can be traced directly to organic causes. In other instances, they appear to originate in certain kinds of family communication patterns. The several causes of those symptoms that have been identified and their minimal prognostic importance suggests that they are a nonspecific response to a variety of conditions and not necessarily part of a longstanding process.

2. Negative symptoms, on the other hand, tend to be associated with chronicity. It is not clear, however, whether negative symptoms and the process they reflect are the source of the chronicity, the result of it, or a combination of both relationships.

3. Disorders of personal relationships have their own antecedents and have important prognostic implications for future functioning in this area and for outcome of positive and negative symptoms as well. In this way disorders of social relationships appear to represent a process with important implications for all of the schizophrenic manifestations. [pp. 68-69]

The key concepts here, including the positive-negative dichotomy, are similar to those used by Wing and colleagues in the MRC Social Psychiatry Unit and those which we have adopted at Northwick Park. Specifically, the concept that positive and negative syndromes represent different components of the process and that the negative component is less variable and more closely associated with poor long-term outcome than the positive component is common ground. On the other hand, the necessity to postulate a third component of "disordered personal relationships" and, by implication, to suggest that this, like the positive and negative syndromes, has its own underlying disease process is not clearly established. Nor does it appear that the

psychological connections that Strauss, Carpenter, and Bartko favor are necessary to the concept.

Thus, the case for two (but not clearly for three) processes was well argued by two separate groups on the basis of the differing time courses of two clusters of symptoms. Both groups recognized that some symptoms (e.g., thought disorder) did not fit easily into one or other category.

Strauss, Carpenter, and Bartko (1974) draw attention to an earlier usage of the positive-negative symptom concept in schizophrenia. Snezhnevsky (1968) wrote that

Symptoms that contribute to the different schizophrenic syndromes may be pathologically productive, or so-called positive. Alternatively they may be negative symptoms, expressive of "flaws," defects and disintegration. Both types combine as a unit, exhibiting organic interdependence and constituting the elements of a syndrome structure However, although they form a unit, the positive and negative disturbances are not equivalent to each other. In simple schizophrenia as well as in remissions after acute attacks, negative symptoms may sometimes emerge alone without coincident positive ones. I.F. Ovchinnikov [in 1966] has pointed out that the positive and negative symptoms are disposed as if on two levels. The positive is the higher level and is characterised by marked variability The lower or negative level by contrast is invariable The invariability of the negative disturbances is very clearly demonstrated during contemporary therapy with modern psychotropic drugs. As a result of therapy, the positive disturbances undergo some degree of change and become more rudimentary. In some cases they may disappear altogether, and modern therapy may create a barrier to the emergence of certain features, for instance, of catatonia. The negative disturbances, however, are refractory to therapy \

and do not change. They may, nevertheless, become usually to a certain extent compensated. [pp. 432-433]

These quotations make it clear that the adjectives "positive" and "negative" had been adopted in relation to the symptoms of schizophrenia earlier in the Russian than in the Western literature. The concept of the relationship between the groups of symptoms outlined by Snezhnevsky is closely similar to that which has been later adopted elsewhere—e.g., at Northwick Park. Since Carpenter, Snezhnevsky, Strauss, and Wing all contributed to the World Health Organization International Pilot Study of Schizophrenia, one may suppose that this project played a role in disseminating the concept.

The concept of the two syndromes (Crow 1980; Crow et al. 1982a) owes much to this background but adds predictions concerning the nature of the underlying processes, and an explanation of why one group of symptoms is more fixed than the other (that it is related to structural brain changes). There was also greater emphasis on intellectual impairment (arising from studies of Crow and Mitchell 1975, Crow and Stevens 1978, and Owens and Johnstone 1980) as a possible correlate of "organic" deficit than is apparent in the earlier concepts.¹

The definition of positive and negative symptoms is clearly crucial to these concepts. My suggestion as to the strategy we should follow is that having arrived at the concept

that there are two (or at least two) syndromes, and that these have different clinical and biological correlates, we should not assume that every symptom need be categorized as positive or negative. Rather, we should adopt a narrow definition and look for those symptoms that correlate well with the defect state (or clinical poverty syndrome) on the one hand or with the florid syndrome of the acute episode on the other. Poverty of speech and flattening of affect seem good candidates for the former, and delusions and hallucinations for the latter syndrome.

Definition of Negative Symptoms

The concept that the definition of negative symptoms should be narrow is in direct contrast to the strategy adopted by some contributors to this volume, especially Andreasen and Sommers. Thus, Andreasen includes as negative symptoms, in addition to affective flattening and poverty of speech, "avolition and apathy, anhedonia and asociality, and attentional impairment." Of these additional symptoms, some (e.g., apathy and asociality) are complex and might well be thought sometimes to occur as a secondary consequence of positive symptoms, anhedonia (if it can be distinguished from affective flattening) might well be thought related to depression, and attentional impairment (as Cornblatt and colleagues have shown) may be more closely related to positive than negative symptoms. Sommers includes "emotional" as well as social "withdrawal" (an issue that has been dealt with by Angrist, Rotrosen, and Gershon 1978b; see below) and states that the terms positive and negative "imply nothing regarding either pathophysiology or the necessary

relationship between positive and negative symptoms" (pp. 364-365), both of which issues are seen as remaining open to empirical investigation. She then goes on to assert that the terms "residual symptoms" or "defect/deficit state" should not be equated with negative symptoms. This sounds an admirable counsel of scientific purity until one considers the problems in arriving at an independent definition of what constitutes a "true" negative symptom. As Sommers recognizes, an appeal to clinical authority is unsatisfactory. So also is the simple concept of loss of normal function. For example, if the net is thrown as wide as Andreasen and Sommers sometimes seem to favor, it will include such features as job loss and marital failure. This is far too inclusive to be interesting.

These issues are also relevant to other contributions. Thus, Solomon Goldberg, in his defense of the concept that negative symptoms respond to neuroleptic drugs, includes as negative symptoms (which he apparently has no qualms in equating with Bleulerian fundamental symptoms) indifference to the environment, apathy, hebephrenic symptoms, inappropriate affect, poor social participation, poor self-care and "confusion." Carpenter, Heinrichs, and Alphs are surely correct to insist on their distinction between primary and secondary negative symptoms. According to this view, several of the above symptoms, and particularly poor social participation and self-care, can be seen as potentially secondary to positive symptoms.²

¹ It should be noted that in a followup study of patients in the community (Johnstone et al. 1981), by contrast with the earlier inpatient study, cognitive impairment assessed on the Withers and Hinton Battery correlated with both positive and negative symptoms.

² "Loss of drive", included in the original two-syndrome concept (table 1) but not rated on the Krawiecka scale may well belong to this category.

We were well aware of this problem when we reported the findings of our trial of the isomers of flupenthixol. The first reference is to the important analysis of the findings of the National Institute of Mental Health trial to which Goldberg rightly draws attention (Goldberg, Klerman, and Cole 1965). In the discussion section of our article (Johnstone et al. 1978a) is the following paragraph:

Improvement in individual symptoms was largely confined to "positive" symptoms [figure 2 of Johnstone et al. 1978a]. Both non-specific and "negative" schizophrenic symptoms showed little tendency to improve and no differential response to drug therapy. Thus the scope of the antipsychotic effect may be more limited than was suggested by an analysis of the 1964 National Institute of Mental Health trial (Goldberg et al. 1965), in which the benefit of neuroleptic drugs appeared to be as great on some *negative features* of the disease (e.g. social withdrawal, lack of self-care) as on the positive symptoms. *Negative symptoms* (identified in a clinical interview rather than on behaviour ratings as in the earlier study) are uncommon in acute schizophrenia but are prominent in the "defect state" in which neuroleptics may be less effective (Letemendia and Harris, 1967).

This view is compatible with those of Carpenter, Wagman, and Heinrichs (submitted for publication, 1984) and Angrist, Rotrosen, and Gershon (1980a), who adopt a narrow definition of negative symptoms to identify the nondrug-responsive component. Affective flattening and poverty of speech (defined in an interview that allows one to exclude symptoms with which these might be confused) appear to be the two symptoms that fall most consistently in this category.

A most notable departure in the opposite direction is the statistical

reanalysis by Gibbons et al. (this issue) of the clinical data that Solomon Goldberg and colleagues originally collected. As Goldberg has noted, these ratings have already yielded the conclusion that all symptoms of schizophrenia, as assessed by these scales, are responsive to neuroleptic medication. According to Gibbons' statistical retreatment, three syndromes of "negative symptoms" are present. One of these loads highly on "fixed facial expression" but also on "apathy toward treatments" and "apathy toward environment," and another loads on "fixed facial expression" as well as "poverty of speech" but also loads on "thought blocking" (surely a positive symptom when properly assessed) and "slow movement" (from which the authors derive their factor label of "retardation"). The most surprising conclusion reached by Gibbons and colleagues concerns their "Bleulerian factor 3," which includes "incoherent speech, irrelevant speech, wandering speech, and inappropriate affect." It is difficult to envisage how these speech abnormalities are distinguished from each other, but more difficult still to understand how all these symptoms can be classified as negative. Certainly our own findings, and indeed those of the trial from which the data of Gibbons et al. were taken, suggest that these symptoms are neuroleptic-responsive. To describe these symptoms as negative appears to be stretching the concept much too far. Only by equating the concept of negative symptoms with Bleuler's fundamental symptoms (some of which are notoriously difficult to define), presumably on the basis of a Jacksonian logic that negative symptoms are bound to be more fundamental than other types of symptoms, can this be understood.

Gibbons et al. appear to have been led up the garden path by Hughlings Jackson and dropped in the pond by Eugen Bleuler.

In all these studies, much depends on how symptoms are defined and how carefully they are rated. On p. 368 of Sommers' contribution occurs a statement which aroused my curiosity. Discussing the need for defined norms, Sommers writes that "In the absence of such standards, raters must rely on their own experience and clinical intuition (a situation which suggests that raters should typically be among the most, rather than the least, trained and skillful members of the research team)." Does this mean, one is bound to ask, that the ratings in some American studies are not made by the principal workers themselves? Are ratings sometimes carried out by workers who are not co-authors? If this is the case, perhaps editors should insist that it be made more explicit. It could account for apparent discrepancies between the quality of findings and the interpretations which are placed upon them. In the Northwick Park studies, the raters have been the most, and not the least, clinically experienced of the co-authors.

Many of the problems reduce to the question of what should be considered a negative symptom. As the contributions to this issue of the *Schizophrenia Bulletin* indicate, opinions vary widely. Contrary to the views favored by Andreasen and Sommers, I suggest that no a priori definition of what constitutes a negative symptom will be generally acceptable. What is rated in Andreasen's schedule of negative symptoms seems to me to include a substantial part of the entire range of the diverse consequences of the disease. Sommers also is in search of a Platonic ideal of what constitutes a

"true" negative symptom, but I suspect it is unattainable. Rather, I suggest we should adopt a pragmatic stance and ask what definition of negative symptoms gives us an interesting way forward. Already we have the suggestion, explicit in the two-syndrome concept but present earlier in the working hypotheses of Wing, Strauss, and their colleagues, that among the manifestations of the disease labeled as negative are some that are better correlated than the more obvious positive symptoms with chronicity and poor long-term outcome. Symptoms included in this category are clearly flattening of affect and poverty of speech. A worthwhile question is whether there are other symptoms that can be reliably assessed which are as good or better. One can also ask how

these particular symptoms are best assessed either in a research interview or in clinical practice.

The two-syndrome concept also includes the proposition that those symptoms which correlate with chronicity are less responsive than positive symptoms to neuroleptic drugs. The way forward for those, like Goldberg, who maintain the single dimension view of pathology, is to demonstrate that negative symptoms, even when defined strictly as above, are just as responsive to neuroleptics as positive symptoms. Indeed the original NIMH trial could be further analyzed along these lines because it appears that among the ratings made available to Gibbons et al. were assessments of fixed facial expression and poverty of speech. These items were not separately

analyzed in the article to which Goldberg refers. How were they actually rated? Were the drug-placebo differences with respect to these symptoms as great as for positive symptoms and "secondary" negative symptoms such as lack of self-care and social withdrawal?

Does the Two-Syndrome Concept Hold Up?

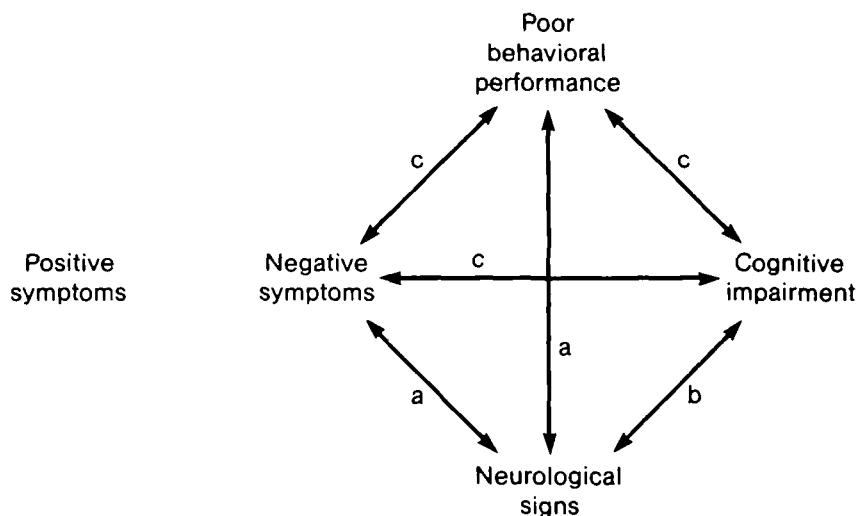
A number of recent investigations are relevant and address issues other than those already considered:

1. Are positive and negative symptom components independent variables? The most extensive study of this issue is the survey of 500 patients with a Feighner diagnosis of probable schizophrenia in Shenley Hospital (our area mental hospital in Northwest London) reported by my colleagues, Owens and Johnstone (1980). These workers assessed mental state with the Krawiecka scales and also obtained ratings of behavioral impairment (from nursing staff), and of neurological and cognitive status.

From a correlational analysis the main findings (figure 1) were significant interrelationships among negative symptoms, intellectual impairment, poor behavior, and the presence of neurological signs. These symptoms were unrelated to physical treatments, and to the presence of positive symptoms.

Thus, in this population of chronic institutionalized patients, positive and negative symptom components (defined on the Krawiecka scale) are relatively independent variables. This is essentially in agreement with the findings of Cornblatt et al. (this volume) and Lewine, Fogg, and Meltzer (1983) but in disagreement with the proposal of Andreasen that positive and negative symptoms be treated as a single continuum.

Figure 1. Interrelationships between negative symptoms and other characteristics



Significant relationships between various parameters in a population of 500 inpatients with chronic schizophrenia (from Owens and Johnstone 1980). Negative symptoms are significantly related to intellectual impairment and behavioral disturbance, and each of these features is related to the presence of neurological signs, including abnormal involuntary movements. This constellation thus corresponds to the type II syndrome. In this population none of these features are related to the presence of positive symptoms (the type I syndrome).

a: $p < .02$; b: $p < .01$; c: $p < .001$.

Assuming that it is true that these are indeed independent dimensions, it is worth considering some limitations on the situations in which this might be established. Thus, for instance, it can clearly only be demonstrated in a population restricted to patients with schizophrenia—if other patients are included, the two groups of symptoms (because they are presumably at least more frequent in, although not specific to, patients with schizophrenia) will tend to correlate together. Secondly, because some negative symptoms (e.g., poverty of speech in its extreme form of mutism) make positive symptoms difficult to elicit, a spurious negative relationship between positive and negative symptoms, such as that postulated by Andreasen, may be recorded (Johnstone, *in press*).

2. Do negative symptoms identify the nondopaminergic component? Beside the trial of the isomers of flupenthixol (Johnstone et al. 1978a), the study most relevant to this issue is that of Angrist, Rotrosen, and Gershon (1980a, 1980b). These workers found that symptom exacerbation by amphetamine predicted potential response to neuroleptic drugs (Angrist, Rotrosen, and Gershon 1980b) in conformity with the dopamine hypothesis. In a reanalysis of individual Brief Psychiatric Rating Scale (BPRS) symptom scores, they found that positive symptoms were exacerbated by amphetamine and improved by neuroleptics, while negative symptoms (after emotional withdrawal was excluded as a "secondary" negative symptom) showed little response to either drug (Angrist, Rotrosen, and Gershon 1980a).

3. Are negative symptoms associated with poor long-term outcome? Are they more persistent than positive symptoms?

This issue is addressed by Pogue-Geile and Harrow (this issue). Also relevant is the study of Pfohl and Winokur (1982) of 52 institutionalized patients from the Iowa-500 sample followed for the presence or absence of negative and positive symptoms over a period of 35 years. Included as negative symptoms were social impairments as well as poverty of speech, flattening of affect, and hypoactivity or catatonic motor behavior. An overall analysis (table 2) indicates that in general negative symptoms are of later onset and more persistent than positive symptoms. In this study a high prevalence of cognitive impairment was noted as in previous studies (Crow and Mitchell 1975; Crow and Stevens 1978; Owens and Johnstone 1980), and these impairments, like negative symptoms, were of late onset and tended to persist. Also of interest is the finding that impairments of self-care were more likely to resolve than some negative symptoms (e.g., flat affect) and cognitive and memory deficits.

4. Are negative symptoms associated with structural brain changes? A number of CT scan studies have now been completed. With one or two exceptions, they are in agreement with the original finding that, by comparison with age-matched controls, some patients

with chronic schizophrenia have a degree of ventricular enlargement (for review, see Crow and Johnstone, *in press*).

Some studies (e.g., Johnstone et al. 1976, 1978b; Rieder et al. 1979; Donnelly et al. 1980; Golden et al. 1980) have found ventricular size to be significantly related to intellectual impairment, others to poor premorbid personality (Weinberger et al. 1980b) or treatment resistance (Weinberger et al. 1980a).

However, in a recent study (Owens et al. 1985) of 110 patients with chronic schizophrenia, lateral ventricular enlargement was not significantly related to negative symptoms and intellectual impairment (in both cases there was a U-shaped relation, with some patients with either feature having small ventricles) but was significantly associated with behavioral deterioration (as in Haug 1962, 1982), absence of positive symptoms, and the presence of abnormal involuntary movements. Ventricular enlargement was unrelated to past insulin coma, electroconvulsive therapy, or neuroleptic medication.

Although some studies (e.g., Takahashi et al. 1981; Gross, Huber, and Schuttler 1982; Kling et al. 1983; Williams et al. 1985) have found ventricular enlargement to be associated with negative symptoms,

Table 2. Time of onset and persistence of positive and negative symptoms in chronic schizophrenia¹

	Onset		Persistence	
	Early	Late	No	Yes
Symptom classification				
Positive	10	1	7	4
Negative	4	10	1	13
<i>p</i> value (Fisher's exact)	0.004		0.007	

¹ Reprinted, with permission, from Pfohl and Winokur (1982).

this has not been a consistent finding. Rather, there is a general tendency for ventricular enlargement (as assessed by CT scans) to be related in different studies to one or more of the components of the type II syndrome—behavioral impairment, intellectual loss, negative symptoms, and abnormal involuntary movements.

One possibility is that, as suggested strongly by a recent post-mortem study (Brown et al., in press), lateral ventricular enlargement, as seen on CT scan, reflects only indirectly more substantial structural changes taking place in the temporal lobe. If these could be directly assessed, better correlations with clinical variables might be obtained.

5. Are there neurochemical correlates of the two syndromes? Because a number of patients included in the Owens and Johnstone (1980) survey have subsequently died, we have been able to examine the relationships between positive and negative symptoms assessed in life and a number of neurochemical variables. The principal findings to date are:

- D₂ receptors (assessed by ³H-spiroperone binding) are significantly ($p < .01$) related to positive but not to negative symptoms (Crow et al. 1981b).

- The enzymes dopamine- β -hydroxylase and choline acetyltransferase are not reduced in patients with negative symptoms (Crow et al. 1981a). Thus, the type II syndrome differs from Alzheimer's disease in which both of these enzymes (markers of adrenergic and cholinergic neurons, respectively) are reduced (this is relevant to the predictions discussed by Carpenter, Heinrichs, and Alphas, this issue.

- In a study of six neuropeptides (Ferrier et al. 1983; Roberts et al. 1983), there were no striking overall differences between patients with schizophrenia and controls, but in patients with negative symptoms cholecystokinin (CCK) content was found significantly reduced in hippocampus and amygdala, and somatostatin content reduced in hippocampus. Since CCK and somatostatin are located in amygdalo-hippocampal projections, and in hippocampus in small interneurons in the pyramidal cell layer, these changes may reflect local neuronal losses.

6. Are there electroencephalographic (EEG) correlates of the type II syndrome? Itil et al. (1975) report a study that apparently is relevant to this issue. On the basis of a computerized analysis of EEG recordings, they concluded:

"Therapy resistant" schizophrenic patients were characterized by a lesser degree of very fast beta activity, more alpha waves and slow waves, higher amplitudes in computer EEG and a lesser degree of acute (florid) psychotic symptomatology but more "negative" symptoms such as motor retardation and blunted affect.

A Revision of the Two-Syndrome Concept

In the light of recent findings, and to render the concept more challenging as a hypothesis, some modest extensions are indicated (table 3). These include particularly the notion that the structural changes that are postulated to underlie the type II syndrome are located in the temporal lobe. This is suggested by the recent post-mortem study (Brown et al., in press) and also accommodates the findings of the investigation of

neuropeptide content (Ferrier et al. 1983; Roberts et al. 1983).

The suggestion is also added that abnormal involuntary movements rather than being (as is often assumed) a late effect of neuroleptic medication (implicit in the concept of "tardive dyskinesia") are a component of the type II syndrome. The notion that such movements are necessarily related to neuroleptic medication has already been challenged (Brandon et al. 1971; Owens, Johnstone, and Frith 1982), as has the view that an irreversible component of such movements is attributable to such medication (Crow et al. 1982b, 1983). The view proposed here that they are part of the type II syndrome is consistent with Kleist's concept of parakinetic catatonia (Waddington and Crow, in preparation), and with observations that these symptoms correlate with other components of the type II syndrome, e.g., intellectual impairment, negative symptoms (Owens and Johnstone 1980; Waddington et al., in press), and ventricular enlargement (Owens et al. 1985) that cannot be attributed to past neuroleptic medication.

The type II syndrome is referred to as the Pinel-Haslam syndrome because these authors were probably the first to provide clear descriptions of what we would now recognize as schizophrenia (Pinel 1809; Haslam 1809). In each case they describe illnesses in which negative symptoms and intellectual decline rather than positive symptoms are prominent. The type I syndrome, on the other hand, is attributed, perhaps a little facetiously, to E. Bleuler as it was he, more so than Kraepelin, who asserted that true intellectual impairment does not occur in the "group of schizophrenias" (Crow and Johnstone 1980).

Different Syndromes, Not Different Diseases

Andreasen (this issue) makes much of the distinction between diseases and syndromes, and writes:

Early formulations of the positive vs. negative distinction failed to discuss the issue of the "mixed" patient. Positive and negative symptoms were treated as if they were distinct entities [p. 385]

These strictures appear to apply particularly to Andreasen (1982) entitled "Negative vs. Positive Schizophrenia: Definition and Validation."³

Such attempts to subdivide schizophrenia are not apparent in the work of Wing, Strauss, and their colleagues referred to earlier, and in Crow (1980) is the following:

Episodes of type I symptoms may be followed by development of the type II syndrome and both may be present together. Type II symptoms, however, define a group of illnesses of graver prognosis. They occasionally occur in the absence of the type I syndrome (for example in "simple schizophrenia) [p. 68]

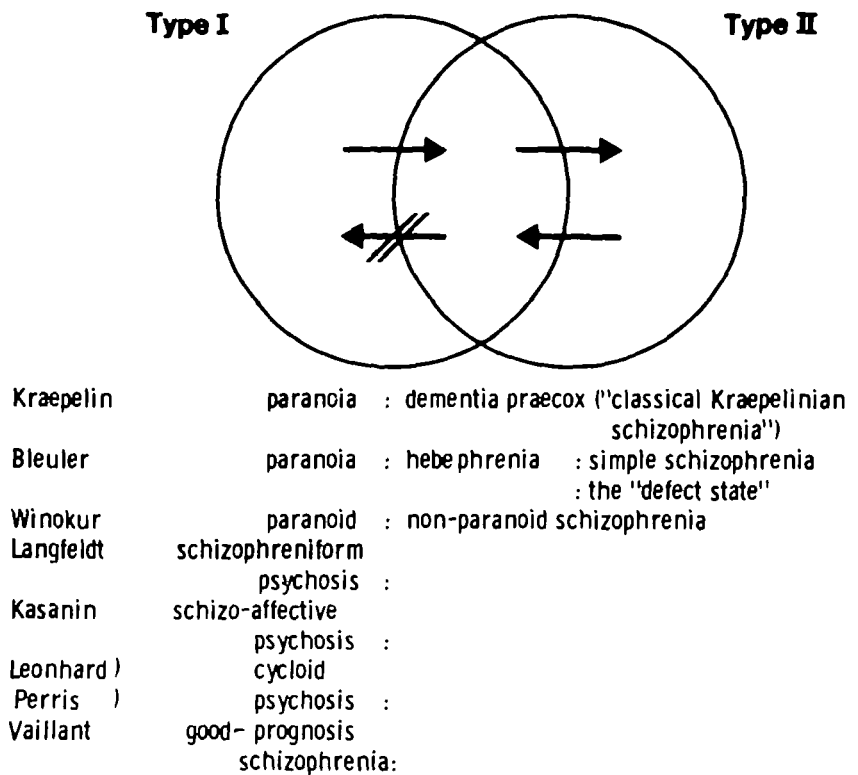
The view that a negative symptom component can either precede or succeed episodes of positive symptoms and that it is a more stable, and less readily reversible component of the manifestations of schizophrenia is implicit in the

formulations of Snezhnevsky, Wing, Strauss, and their colleagues. Strauss, Carpenter, and Bartko (1974) also drew attention to the relationship between the presence and absence of the negative symptom component and the process-reactive, amorphous-fragmented, good-poor premorbid, and schizophrenia-schizophreniform psychosis distinctions of other authors. I have attempted to illustrate the possible temporal relationships between the two syndromes and their correspondence to other concepts by a scheme of

overlapping circles in a Venn diagram (figure 2).

In this figure, the arrows indicate possible progression of symptoms with the passage of time. Thus, some illnesses present with positive symptoms as in the left segment of the figure. If they remit, they tend to be labeled as "schizophreniform," "schizoaffective," or "reactive." If they persist and no negative symptoms appear, they can be considered as chronic paranoid illnesses (according to the paranoid-nonparanoid dichotomy of Tsuang

Figure 2. Relationship between types I and II syndromes as overlapping constellations of symptoms, and changes that can occur with time (Indicated by arrows)



Also shown are possible relations of the 3 symptom patterns (defined by the intersection of the circles) to other diagnostic subclassifications of schizophrenia (from Crow 1983).

³The view (Andreasen, this issue) that positive symptoms are related to an excess, and negative symptoms to a deficit, of dopaminergic transmission, is in difficulty in explaining how patients can have both types of symptom at the same time. This problem is recognized (Andreasen, p. 383) but no solution offered. It appears the difficulty is fatal for the single dimension dopaminergic hypothesis.

and Winokur 1974). Illnesses in which negative symptoms also appear (or are already present) will tend to be labeled as "nonparanoid," "true," "process," or "classical Kraepelinian" schizophrenia. In some of these illnesses, positive symptoms will remit (as Pfohl and Winokur, 1982, have documented) leaving the "pure deficit" type II syndrome (right-hand segment of Venn diagram). In some cases, positive symptoms reappear. However, the crossed arrow between the middle and left-hand segments of the diagram is intended to indicate the relative resistance to remission of the components of the type II syndrome, i.e., primary negative symptoms and intellectual impairment.

It seems likely that negative symptoms do sometimes remit. Goldberg (this issue), Pogue-Geile and Harrow (this issue), and Pfohl

and Winokur (1982) provide examples. If such symptoms are defined loosely and include those that would be regarded by Carpenter, Heinrichs, and Alphas (this issue) as secondary, this is not surprising. The more interesting question is whether primary negative symptoms and intellectual impairments ever remit. I suspect that they occasionally do, but it is a relatively unusual event, and one which deserves to be well documented. A problem is to define such symptoms as "true" (or primary) negative symptoms. One approach is that of Huber and colleagues (Huber 1966; Gross, Huber, and Schüttler 1982) to what they refer to as the "irreversible pure defect syndromes." These are defined as irreversible when they have been present without change for 3 years. Such a definition, of course, limits their use as prognostic indices but, as

with the *DSM-III* (American Psychiatric Association 1980) definition of schizophrenia, perhaps for some purposes it is necessary to take into account duration.

Etiological Implications

Since negative symptoms, or more generally the type II syndrome, define a group of patients with schizophrenia who are doing badly rather than a separate disease entity, the distinction does not have clear etiological implications. Perhaps as Winokur and colleagues have suggested, genetic factors are relevant to the development of nonparanoid types of illness as well as to schizophrenia in general. In other words, it may be that patients with particular genes in addition to those which predispose to schizophrenia are liable

Table 3. Modified two-syndrome concept¹

	Type I	Type II
Characteristic symptoms	Delusions, hallucinations (positive symptoms)	Flattening of affect, poverty of speech (negative symptoms)
Response to neuroleptics	Good	Poor
Outcome	Potentially reversible	Irreversible?
Intellectual impairment	Absent	Sometimes present
Abnormal involuntary movements	Absent	Sometimes present
Postulated pathological process	Increased D ₂ dopamine receptors	Cell loss (including peptide-containing interneurons) in temporal lobe structures (hippocampus, amygdala, and parahippocampal gyrus)
Eponym	E. Bleuler	Pinel-Haslam

¹ Modified from Crow and Johnstone (1985).

to develop negative symptoms and intellectual defects. I have argued (Crow 1984) that the retrovirus/transposon hypothesis is more parsimonious than a gene-environmental factor interaction in explaining the etiology of schizophrenia, and have put forward a case for a common etiology for schizophrenia and manic-depressive psychosis. According to this view, the type II form of schizophrenia might be seen as at one end of a continuum of severity of outcome, i.e., as that subgroup of patients with psychosis who either have the most severe structural changes in the brain or have lesions located in sites where they are least easily compensated.

Solomon Goldberg (this issue) offers the alternative hypothesis that a subgroup of patients with schizophrenia have a quite different ("organic") etiology from the majority of patients and that it is this group who show ventricular enlargement, intellectual impairments, and poor response to neuroleptic medication. He also argues (along with R.M. Murray and coworkers) that this group have a less genetic form of the disease. This view encounters several problems, among which are: (1) the relatively high prevalence of severe cognitive impairments in patients with chronic schizophrenia (Stevens et al. 1978; Owens and Johnstone 1980), (2) the strong association between negative symptoms and cognitive deficits (table 2), and (3) the fact that the relation between family history and ventricular enlargement depends critically upon the (arbitrary) line that is drawn between normal and abnormal ventricular size (Owens et al. 1985).

Two articles in the present issue (Sommers and Carpenter, Heinrichs, and Alphs) refer to the concept that

negative symptoms are due to institutionalization. This was examined in the study of Johnstone et al. (1981) in which it was established that when age and duration of illness are taken into account, negative symptoms are as common in patients (defined by the Feighner criteria) who have been discharged into the community after inpatient admission as in patients who have remained in hospital. Intellectual impairments, however, were greater in the latter group. A further investigation (Johnstone et al. 1985) established that in a small group of institutionalized patients with chronic manic-depressive psychoses (defined by the Feighner criteria), negative symptoms did occur (although less frequently than in a comparable group of patients with schizophrenia), and cognitive impairments were present in both groups. Thus, some components of the defect state are present in psychoses other than schizophrenia.

Conclusions

The concept of two syndromes in schizophrenia arose from the necessity to postulate more than one dimension of pathology underlying the disease—a reversible (and potentially neuroleptic-responsive) component and a sometimes progressive and relatively irreversible component associated with the deficit state and poor long-term outcome. Negative symptoms (narrowly defined as in the modified Krawiecka scale) appear to be more closely related to the latter component, as also are cognitive impairments (which are common in chronic schizophrenia), abnormal involuntary movements, and behavioral deterioration. These are components of the type II syndrome (which corresponds to the "defect state" or "deficit

syndrome") that is postulated as more closely related than positive symptoms (the type I syndrome) to the structural brain changes described in pneumoencephalographic, CT scan, and recent post-mortem studies. The type I syndrome represents the potentially neuroleptic-responsive and reversible component, and may be associated with a disturbance of dopaminergic transmission. In post-mortem brain tissue from patients assessed in life for positive and negative symptoms, numbers of D₂ receptors are significantly correlated with positive but not negative symptoms, and CCK and somatostatin content of hippocampus and CCK content in amygdala are reduced in patients with negative symptoms. The type II syndrome may be a consequence of structural changes occurring in the temporal lobe.

The two syndromes are regarded as relatively independent processes which may coexist in the same patient but follow different time courses; they are assumed to be different manifestations of the activity of a single pathogen.

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