TILAK VENKOBA RAO ORATION

NEGATIVE SYMPTOMS IN PSYCHIATRY: PSYCHOBIOLOGICAL & PSYCHOSOCIAL ASPECTS

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The Tilak Venkoba Rao Oration is for the young scientist and before I deliberate on my subject it is my honoured right to speak for the young psychiatrists in our country. I have observed and experienced that the young psychiatrist is the most unfortunate person during his academic career. He is often discouraged from all quarters, so much so, that he feels that he has to struggle in order to do any work. Not to work and not to aspire are the easiest ways. The young psychiatrist faces numerous uphill obstructions all along and perhaps may be frustrated and fall into the streamline of complacency and academic politicking. For the advancement of our discipline and science, undoubtedly, the younger scientists have to take lead and shoulder the responsibilities. The demoralisation, discouragement and the crushing of the younger scientists is thus very hazardous. In light of these, I feel proud and honoured to have been awarded this opportunity to present my work on negative symptoms. No words would be sufficient to thank Professor Venkoba Rao for having initiated this award, and I would like to thank Professor Nandi and the judges of the awards committee for this award being given to me. I am also grateful to numerous colleagues who have worked with me on negative symptoms. After these few words about negative attitudes towards young psychiatrists I would present my research work on Negative Symptoms in Psychiatric disorders.

In the nineteen eighties there have been many subjects which have attracted attention, by far maximum research interests have been captured by the study of negative symptoms in psychiatric disorders. Psychiatric researchers have taken up the challenging task of redefining negative symptoms, attempts at validating the concept and devising measures for their reliable quantification. Last and not the least, is the unfathomable challenge of the treatment of negative symptoms, which can be very frustrating. It is really commendable that numerous researchers in different parts of the world are concentrating on a psychopathological aspect which is strife with controversy and challenge. Thus the terms positive and negative symptoms have slipped into the language of contemporary psychiatry with comparative ease. It is not uncommon for these expressions to be used with little explanation, with the implicit understanding that their meaning is understood and that somehow they are of value to our knowledge of psychopathology (Trimble 1986).

The concept of negative symptoms is both rather old and rather new. Writings of Kraepelin (1919) and Bleuler (1950) indicate that they had perceived negative or deficit symptoms to be the underlying fundamental abnormality. Both concluded that, in addition to a deteriorating course that did not permit a full recovery, patients suffering from schizophrenia experienced a loss of

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cognitive, affective, volitional, and attentional functions.

The credit for the introduction of these terms is usually given to Hughlings Jackson and the concept of positive and negative symptoms is clearly outlined in several of his papers: "The negative element in the symptomatology is what the epileptic discharge produces; it is the dissolution...the positive element is physical activity of the lower nervous arrangements, which are, except for overactivity, healthy" (Jackson 1881). Implicit in these ideas are that positive and negative symptoms are closely intertwined such that they both occur contemporaneously, the pathology that gives the negative symptoms at the same time allowing expression of the positive symptoms.

The variety of words used to refer to the group of negative symptoms highlights some of the conceptual problems that remain, however. They are variously referred to as fundamental, deficit, or negative symptoms. "Fundamental" implies that they are the basic symptoms in a disorder and in some sense pathognomonic of it. The word "deficit" implies that these symptoms represent a loss of function and sometimes imply an irreversible loss as well. The term "negative symptoms" is perhaps the least specific; it also implies the loss of function, but carries no implications about diagnostic specificity or irreversibility. Sometimes the terms "core negative symptoms" or "Primary negative symptoms" are used in order to identify that subset of negative symptoms that are more specific to schizophrenia and are probably due to some as yet unrecognized neural mechanism characteristic of this illness.

Methodological Issues:

In light of the putative clinical and theoretical importance of negative symptoms and the controversies surrounding their assessment, there is a need for adequate means of making systematic assessments.

Measurement: Those interested in this area have relied on the analysis of separate symptoms and signs, with the notable exception being the work of Andreasen (1981). She devised the Scale for the Assessment of Negative symptoms (SANS) which has subsequently been widely used in U.S., India, and Europe. Lewine and colleagues (1984) used data obtained from well established psychiatric instruments administered regularly and used the Rasch model in the construction procedure in the development of the symptom scale. They derived items from the Schedule for Affective disorders and Schizophrenia--current (SADS-C) and the Nurses' Observation Scale for Inpatient Evaluation (NOSIE). Many researchers have used the Brief Psychiatric Rating scale items for assessing negative symptoms. Other instruments which have been used for assessment of negative symptoms are the Krawiecka scale, Psychopathology Rating scale and the Psychiatric Assessment Interview, PAI. In most of my research on negative symptoms I have used Andreasen's Scale for Assessment of Negative symptoms.

Reliability and Validity: The validity of SANS was reported by Andreasen and Olsen (1982). There was good internal consistency for items as well as subscales. The interrater and test–retest reliability was assessed in the Indian set up, and found to be reasonably high on most components by us (Mathai et al. 1984).

Stability of Negative Symptoms: We found negative symptoms to remain stable over a period of one month (Mathai et al. 1984) and even after a period of two years (Michael et al. 1986) in a group of patients diagnosed as chronic schizophrenia. The stability of negative symptoms in chronic schizophrenias could partly be due to lack of adequate treatment models presently.

Prevalence and nature of negative symptoms: Though negative symptoms are
considered important clinical features of schizophrenia, they are neither pathognomonic of it, nor specific to it. Their frequency in other psychiatric illnesses, as depression has been reported by many workers (Andreasen and Akiskal 1983, Pogue-Geile and Harrow 1984, Chaturvedi and Sarmukaddam 1985, a). In manic and acute schizophrenic episodes also negative symptoms have been described. High negative symptom scores were also observed in simple schizophrenics, schizotypal personality disorder cases and mentally retardates.

In our study of 30 chronic schizophrenics, according to DSM III diagnosis, mild negative symptoms rated on SANS were observed in more than 75% of the cases and severe intensity of negative symptoms were noted in nearly 2/3 of the cases, and fulfilled the criteria of Negative Schizophrenia as described by Andreasen and Oslen (1982) (Chaturvedi et al. 1984). Lindenmayer et al. (1984) reported predominant negative symptoms in nearly 25% of acute schizophrenic patients. We had also observed that some acute schizophrenics did have marked negative symptoms, especially affective flattening, impaired attention and poverty of speech.

Study of negative symptoms in depressive disorders has also attracted attention, though not to the same extent as for schizophrenia. Pogue-Geile and Harrow (1984) have reported mild negative symptoms in depressives after an 1½ year follow up. Interestingly, the frequency, nature and prognostic value of some negative symptoms have been examined earlier in neurotic and psychotic depression cases, though these symptoms were not termed as negative symptoms, then. Andreasen (1986) also reported marked negative symptoms in patients diagnosed as major depression. In a study on 34 patients diagnosed as definite, endogenous major depression according to R.D.C. (Spitzer 1978) we found high mean scores on each of the SANS subscales. The commonest negative symptoms were inability of enjoy recreational activities and interests (77%), inability to enjoy sexual activity and interest (65%), feeling of anhedonia (62%), inability to form friendship and physical anergia (56% each). The negative symptoms were more marked in the younger patients (Chaturvedi and Sarmukaddam 1985).

Negative symptoms have recently been studied in mania also and differences in negative symptoms between patients diagnosed as schizophrenia, mania and depression have been documented by Andreasen (1986). We had examined the differences in negative symptoms between chronic schizophrenics and major endogenous depressions and found that total negative symptom score and affective flattening were higher in the schizophrenic group than depressives. Depressives were more often subjectively aware of the negative symptoms and more often had feelings of anhedonia, avolition and affective flattening (Chaturvedi et al. 1985). In cases of severe neurotic depression we did not find negative symptoms to occur commonly.

PSYCHOBIOLOGICAL ASPECTS

Neurological abnormalities: Crow (1980) has proposed an anatomical model for negative symptoms in which negative symptoms (Crow's Type II symptom syndrome) represent a behavioural manifestation of some structural brain abnormality, such as cortical atrophy. Several studies have explored this hypothesized association between negative symptoms and ventricular enlargement on computed tomography scans (Johnstone et al. 1976, Andreasen et al. 1976, Nasrallah et al. 1983) and other biological variables, such as platelet monoamine oxidase (Lewine and
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Meltzer 1984), with somewhat mixed results. Studies have been generally more unequivocal in finding negative symptoms to be associated with intellectual deficits in chronic schizophrenic patients (Johnstone et al. 1981. Owens and Johnstone 1980). Crow (1980) has suggested that positive symptoms (his type I symptom syndrome) may be caused by a fluctuating, functional dopamine excess, in contrast with the structural brain abnormality hypothesized to underlie negative symptoms.

In one of our study conducted on 30 patients diagnosed as schizophrenia by DSM III Criteria (A.P.A. 1980), 15 each with predominantly positive and negative symptoms. it was found that negative schizophrenics had a significantly higher prevalence of 'soft' neurological signs, especially, with regard to, frontal, parietal, temporal and total lobe scores (Mathews et al. 1985).

C. T. Scan abnormalities: Dilated ventricles and enlarged sulci have been found in patients with predominant negative symptoms (Crow 1982. Seidman 1983). Enlargement of the third ventricle has also been noted. However, no definitive or pathognomonic abnormality has been observed in chronic schizophrenics – either those with positive or with negative symptoms.

Cognitive Dysfunction: Waddington et al. (1985) have in a series of studies documented close relationship between tardive dyskinesia, intellectual impairment and negative symptoms in schizophrenics. The prominent negative symptom in such patients is usually poverty of speech. Negative schizophrenics have been found to have more dysfunctions, especially in the elderly. However, there are no indications of gross deterioration of cognitive functions. A few studies have found almost similar disturbances in schizophrenics with mainly positive symptoms. Signal discrimination attention deficits on psychometric tests were consistently associated with negative symptoms (Nuechterlain et al. 1986). A possible theoretical link between schizophrenic attentional impairment and negative symptoms derives from the recent suggestion that the pattern of deficits in attentional functioning and information processing in schizophrenic patients is consistent with a reduction in available processing capacity (Nuechterlain and Dawson 1984). In our study, chronic schizophrenics who were older in age, had longer duration of illness and continued medications had significantly higher attentional impairment than others (Chaturvedi et al. 1985).

Language Production: Allen (1983) found that contrary to existing conceptions of speech disorder in schizophrenia, both positive and negative speech disorder were found to be marked by poverty of thought, as measured by production of fewer and shorter ideas and lower speech variability. In another study on 45 R.D.C. Schizophrenics, positive and negative thought disorders were equally present in acute and chronic schizophrenics, and paranoid and non–paranoid schizophrenics (Mazumdar and Chaturvedi 1987).

Pre-Morbid Adjustment: There have been definite indications of early developmental delay in milestones, poor scholastic performance, and poor premorbid adjustment in patients with prominent negative symptoms. In our study comparing positive with negative schizophrenia, though a predominance of poor premorbidity was noted, there were no significant differences between the positive symptoms and negative symptoms groups (Mathews, Chaturvedi & Gopinath 1986).

Intellectual impairment: Though no definite intellectual impairment has been
observed in patients with negative symptoms, certain studies did find that patients with negative symptoms had intellectual impairment especially in patients who had demonstrable structural brain damage (Waddington et al. 1986). Patients with negative symptoms tend to have lower educational achievements than those with positive symptoms.

**Dyskinetic Movements:** Patients with dyskinetic orofacial movements, more often had negative symptoms, especially in the elderly (Waddington et al. 1985). In another recent study, almost two-thirds of patients with tardive dyskinesia had high negative symptom scores (Karson et al. 1985). These findings support the proposal that, at least in schizophrenia, subtle organic changes may contribute to vulnerability to the emergence of involuntary movements as well as negative symptoms (Waddington and Youssef 1986, Crow 1980).

**Neurotransmitters Disturbances:** There has been relatively little investigation of the biological correlates of negative symptoms. Certain researchers have proposed that the mechanisms underlying negative symptoms could be neurochemical and therefore potentially reversible. Negative symptoms may be due to a functional deficit in dopamine rather than an excess. Crow et al. (1981) have shown that while the number of D2 receptors is decreased in patients with positive symptoms, patients with negative symptoms have normal numbers of D2 receptors. The enzymes Dopamine beta hydroxylase and Choline acetyl transferase were not found to be reduced in patients with negative symptoms (Crow et al. 1981).

Lewine and Meltzer (1984) had observed an association between high platelet MAO activity and negative symptoms in male patients, thereby possibly implicating the Serotonin system. However, such a relationship was not observed in the studies of Owen et al. (1981) and Brockington et al. (1976).

Other reports observed decreased cholecystokinin content in the hippocampus and amygdala and stomatostatin content in the hippocampus of patients with prominent negative symptoms. Since Cholecystokinin (CCK) and dopamine coexist in the mid brain as co-transmitters, this finding could provide further support for dopaminergic involvement. Also since CCK and stomatostatin are located in amygdalo-hippocampal projections, and in hippocampus in small interneurons these changes may reflect local neuronal loss (Ferrier et al. 1983, Roberts et al. 1983).

However, a number of studies did not find any relationship between platelet MAO activity and negative symptoms. Sex hormones have also been implicated to have a role in the modulation of both platelet MAO activity and negative symptoms in the same direction.

Other parameters which have been investigated are the Dexamethasone suppression tests and smooth pursuit eye movements in patients with and without negative symptoms. Shima et al. (1986) found post dexamethasone cortisol levels to be significantly correlated with the SANS total scores and the non-suppressors were all classified as 'negative schizophrenia'.

**Neuropsychological Defects:** Patients with prominent negative symptoms have been found to have impairment in neuropsychological testing. The pattern of neuropsychological deficits appeared to be consistent with a process characterized by failure in the development of a normal repertoire of cognitive abilities.
Negative symptoms have also been found to be associated with lowered information processing capacity, as already described.

EEG Abnormalities: Though a few reports had mentioned about non-specific EEG abnormalities in patients with negative symptoms, no such difference was observed by us (Mathews, Chaturvedi and Gopinath 1986). We, however, found abnormalities of EEG equally distributed in both the positive and negative symptom groups.

Pharmacological basis of negative symptoms: Drug side effects may mimic negative symptoms e.g. akinesia. Although not well established there is a potentially more fundamental relationship between neuroleptic drug action and negative symptoms. Psychological and behavioural changes similar to negative symptoms have been induced in infrahuman primates and non-psychotic humans by neuroleptic drugs. Although neuroleptics do not produce neuroanatomical lesions, noradrenergic receptor blockade by these drugs would theoretically be functionally equivalent, and, as such, might produce negative symptoms like anhedonia by a similar mechanism. We had observed that certain negative symptoms as inattention, social withdrawal and affective flattening were aggravated by continuous neuroleptic therapy (Chaturvedi et al. 1985, Chaturvedi 1986).

PSYCHOSOCIAL ASPECTS

Social understimulation and institutionalization are other factors considered as influencing production of negative symptoms. Hospital environment has also been blamed to have a role in exacerbating negative symptoms or deficits as avolition and apathy. Andreasen and Oslen (1982) and we in our study on chronic schizophrenia (Chaturvedi et al. 1984) however did not note similar observations. However, the understanding of psychological and psychosocial factors in negative symptoms has received little attention. Carpenter et al. (1985) have described that the trauma experienced by the person with schizophrenia and the possible psychological reactions to that experience, and factors like demoralization may be crucial in many instances of negative symptoms.

Currently, phenomenon such as demoralization and source of “low energy” or poor goal orientation in schizophrenia receive only little attention. The possible roles of social supports, self esteem, hope, coping mechanisms and their aberrations are all crucial pieces for understanding negative symptoms and for their prevention and treatment.

We studied a large group of patients attending day care services and found that they showed improvement in negative symptoms, and about 45% showed reasonably adequate work performance as compared to other schizophrenics. Also their duration of stay in day care centre is comparable to other psychiatric patients (Gopinath et al. 1985, Chaturvedi et al. 1986). In yet another interesting study we constructed a scale for the assessment of Family Distress, due to an individuals symptoms. We found that negative symptoms were more often perceived as distressful as compared to positive symptoms (Gopinath and Chaturvedi 1986).

Duration of hospitalisation of chronic schizophrenics did not have any significant relationship with the severity of negative symptoms or subscale scores (Chaturvedi et al. 1985).

Cultural Differences: These were first noted in the multicentred International Pilot study of Schizophrenia and its 2-year
follow-up. Negative symptoms were not specifically studied in these investigations. Recently, we have compared nature, severity and prevalence of negative symptoms in schizophrenics in India and U.S. where similar instruments and methods have been employed. Significant differences are noted with regard to speech related negative symptoms. Similar comparison for patients with major depression also showed that negative symptoms occur in different cultures, but the type differ depending on the cultural background (Chaturvedi 1986a).

**Prognostic Value of Negative Symptoms:**

Schizophrenia: Most studies have clearly documented poor prognosis of schizophrenia in those who have predominant negative symptoms (Johnstone et al. 1981, Andreasen and Oslen 1982). In India, we have also made similar observations in chronic schizophrenics. This is more related to the underlying brain damage, which coexists (Chaturvedi et al. 1984).

Depression: Depressives with prominent negative symptoms and anhedonia had been found to require a longer duration of treatment, had a poorer outcome, and also they required adjuvants as antipsychotics and electroconvulsive therapies in addition to antidepressants (Chaturvedi and Sarmukaddam 1985; 1986a; 1986b). Negative symptoms have thus been found to have definitely a detrimental influence on the outcome of depression. Retarded depressives are usually believed to have a favourable outcome, but our studies on endogenous depression, revealed that high initial negative symptom scores, unrelated to severity of depression, predicted poorer outcome at one year follow-up. Long term follow-ups also indicate presence of negative symptoms in sub-chronic or chronic forms of depression (Andreasen and Akiskal, 1983). The prognostic value of negative symptoms in other disorders is still under study.

**Conclusions**

The concept of negative symptoms has become increasingly important since it was reintroduced into psychiatric thinking several years ago. As the possible significance of negative symptoms clarified, the complexity of this concept has also become apparent. Genetic, other biological, and many psychosocial factors may interact over time in important ways to generate negative symptoms. It does not seem possible now to provide an integration of the vast number of considerations and complexities that the focus on negative symptoms has generated. The various pathways for understanding these symptoms have become clearer, however, and with this clarity is the increasing possibility of improved prevention and control of these tragic and debilitating phenomenon.

While theoretically appealing, and while supported by considerable evidence, the distinction between positive and negative symptoms in schizophrenia have a number of problems. It is best viewed as a heuristic approach to subtyping schizophrenia that lends itself to hypothesis testing and may be hypothesis generating. There is a possibility that a distinct category of ‘negative depression’ also occurs, which needs confirmation.

The etio-pathogenesis of negative symptoms is still unclear, though the role of structural brain damage, neurochemical mechanism and psychosocial factors have been well recognised. Similarly, the treatment aspects still require definitive trials for the alleviation of negative symptoms.
Future Developments

In dealing with the complex issues related to negative symptoms major progress has been made in describing negative symptoms more reliably and in taking steps toward identifying possible biological correlates. Besides pursuing further the biological aspects two other particularly important directions need to be pursued.

First, the psychosocial factors need to be explored further both in terms of their etiological contributions to negative symptoms and in the way these symptoms influence psychosocial aspects of the evolution of the disorder and recovery.

Secondly, more attention must be focussed on the potential that negative symptoms have for providing an understanding of the interface between biological, psychological and social processes in psychiatric disorders. In these ways the study of negative symptoms may contribute major clues to the nature of psychopathology, its etiologies and its course.

Treatment of Negative Symptoms

The rational for treatment of the negative symptoms of schizophrenia requires a careful differentiation of those secondary to a range of other factors and those that constitute enduring primary or deficit symptoms. Secondary negative symptoms are usually responsive to treatment of the underlying cause. In contrast, there is no intervention currently available with established efficacy in treating deficit symptoms, or the primary negative symptoms (Carpenter et al. 1985).

Various drugs which have been used for the treatment of negative symptoms include neuroleptics, anticholinergic agents, anti-depressants, anxiolytics, amphetamines, L-dopa, etc. Other methods include reducing dosage of neuroleptics.

Other modes of therapies like supportive therapy, psychotherapy, activity therapy, skills training can be tried. There are no well established evidences to support the use of these techniques. It is the challenging task of reducing these negative symptoms in psychiatric disorders which makes the subject so interesting.

Rehabilitation measures and after care services also probably could be useful in minimising negative symptoms.

Critique:

Recently there has been a revival of interest in the study of negative symptoms. Most researchers have quite emphatically pointed out that negative symptoms are not indigenous or characteristic of schizophrenia and are seen in other psychotic disorders and depression as well.

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