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Discussion

The Causality of Depression in Schizophrenia

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The phenomenon of post-treatment depression in schizophrenia has become the subject of considerable controversy regarding its causality (Ananth and Chadirian, 1980; McGlashan and Carpenter, 1976a). But as the recent commentary by Hirsch (1982) emphasizes, the most controversial issue is focused on whether this depression is neuroleptic-induced. Hirsch himself refutes neuroleptic-induction on the basis of various uncontrolled data which seem ostensibly incompatible with this causality. Results indicating that pretreatment depressions appear in a high proportion of recently hospitalized schizophrenics, occur in drug-free patients, and frequently remit or decrease following neuroleptic therapy are cited as evidence contradicting neuroleptic-induction. Hirsch therefore proposes an alternative view: that this post-treatment depression is an integral, "revealed" aspect of the schizophrenia syndrome which arises from the same pathophysiological process (cf. McGlashan and Carpenter, 1976b).

There are several theoretical and methodological issues not addressed by Hirsch, however, which might render this or any theory concerning the causality of this depression premature if not too all encompassing.

(1) Significant pretreatment depression in a recently hospitalized schizophrenic could signify many things. First, by current American criteria (RDC or DSM–III) such a patient might rather receive an "affective" or "schizoaffective" diagnosis, a trend (especially characteristic of research settings) which attempts to mimic the more stringent diagnostic practices of European psychiatry. Yet one might wonder if such practices were operative in the studies quoted by Hirsch as refuting neuroleptic-induction. Knights and Hirsch (1981), for example, indicated the presence of PSE depressive syndromes in a sample of acute schizophrenics which were almost as frequent as their presence in a control sample of hospitalized depressives. The comparatively lesser severity of symptoms in the sample as a whole, furthermore, did not exclude the possibility that, in many patients, severity was equivalent to that found in the depressives. Moller and von Zerssen (1982) likewise reported significant depression in a substantial number of recently hospitalized schizophrenics, 60 per cent of whom were first admissions and 44 per cent acutely precipitated. In the samples reported by Johnson (1981), depression (Hamilton Depression Scale >15) on admission was evident in seven, and preadmission depression (past 2 months) in another 11, of 37 never-treated first illness schizoprenics. A few of these patients, however, had originally been diagnosed for depression, while still others had a history of depression for which they may have previously attended hospital. In another sample of relapsed schizophrenics who had been drug-free for at least two months, 24 of 79 met HDS depression criteria. In addition to the secondary status apparently accorded depression in these patients, the reported use of Schneiderian symptoms as a basis for diagnosing schizophrenia may also be questionable since these symptoms also occur, if less frequently, in manics and psychotic depressives.

Given that many patients in the above studies were initially depressed, findings such as reported by Knights and Hirsch (1981) indicating that initially depressed patients tend to remain depressed after drug therapy are neither unexpected nor evidence against neuroleptic-induction, since neuroleptics might have impaired remission or regression, or ceiling effects on ratings might have limited the ability to determine psychometrically whether symptoms had actually worsened in some patients (see below).

Secondly, since depression is frequently observed as the first sign of relapse in outpatient schizophrenics

maintained on neuroleptics (Floru *et al,* 1975; Hertz and Melville, 1981; Hogarty *et al,* 1979; Mandel *et al,* 1982), it would not be unusual to find that relapsed patients are frequently depressed when rehospitalized. Some pretreatment depressions in recently admitted patients could therefore be neuroleptic-induced.

Third, even among relapsing schizophrenics who previously ceased taking neuroleptics for any time (e.g. Johnson, 1981), the neuroleptic-induction of depressions observed at time of hospitalization cannot be ruled out. This contention is supported by the Casey *et al* (1960) finding that neuroleptics can have long-lasting residual effects which may be depressogenic. In this study, patients were randomly assigned to chlorpromazine (CPZ) (fixed 400 mgs/day) and placebo (plus other drugs), treated for 3 months, and then randomly *reassigned* to these same treatments for another 3 months. After 6 months, patients who were initially assigned to CPZ but subsequently reassigned to placebo were significantly more depressed than patients who, by sequential randomization, were treated with placebo for the entire period. Such residual depressogenic effects might conceivably be due to biochemical changes attending chronic receptor blockade which persist in spite of drug withdrawal. Similar effects may also be responsible for the long delay of relapse following neuroleptic withdrawal in chronically medicated outpatients.

(2) The causes of post-treatment depression in schizophrenia may be heterogeneous, but a substantial proportion of these depressions are probably *pharmacogenetically-induced.* In a recent study (Galdi *et al,* 1981), we reported, in one sample, that schizophrenics who had depressed first-degree relatives were significantly more depressed after 4–6 weeks of neuroleptic therapy than similar patients treated with placebo. Schizophrenics who had schizophrenic first-degree relatives failed to show differences in the effect of neuroleptics and placebo on depression. In a second, uncontrolled sample in which sensitive ratings scales were used, depression increased in patients who had a depressed parent but decreased in patients who had a schizophrenic parent. Yet these subgroups could not be differentiated at pretreatment on the basis of presenting symptoms including depression, in one sample, while in another, patients who had depressed relatives were slightly more depressed, although this was mainly due to higher anxiety. Although we cannot speak to the rigor of the DSM–II criteria applied in these samples where prior psychiatric history was assessed, 70 per cent of the schizophrenics with depressed relatives were described by admitting psychiatrists as being chronically ill. This chronicity indirectly confirmed the poor prognostic character of post-treatment depressions reported by others (Mandel *et al,* 1982). A similar finding from the Hogarty *et al* (1979) study of relapsed schizophrenics maintained on depot neuroleptics, furthermore, supports the view that many of the depressions observed in recently hospitalized schizophrenics may also be pharmacogenetically-induced. In this study, relapsed patients, whose symptoms frequently revealed a distinct "affective quality" on hospitalization, were found to have significantly more affective illnesses in first-degree relatives than nonrelapsed patients.

(3) Post-treatment depressions in schizophrenics which are pharmacogenetically-induced are frequently accompanied by pseudo-Parkinsonism and, less often, akathisia. Our findings revealed more severe demonstrations of these EPS in schizophrenics who had depressed first-degree relatives (some mild EPS also occurred more frequently but failed to reach significance), and correlations between these EPS and depressive symptoms which, though not well coordinated, ranged .49–.79 in these patients. These findings not only implicated neuroleptics in the induction of this depression, but suggested that these more severe EPS may also be pharmacogenetically-induced. The genetic selectivity of these drug-induced symptoms also contradicts past tendencies to trivialize them as simply "drug-induced" or notions that the depression is not a real depression. Our findings instead imply that severe pseudo-Parkinsonism (and possibly akathisia) as well as its correlated depression may result from the interaction of neuroleptics with a genetic defect affecting the nigrostriatal DA system of patients with associated disorders. We applied the terms "pharmacogenetic depression" and "pharmacogenetic pseudo-Parkinsonism" to distinguish these responses, emphasizing their potential diagnostic utility. In this sense, we can agree with Hirsch (1982) as to the pathophysiological significance of this depression.

(4) Post-treatment depressions of the pharmacogenetic (nigrostriatal) variety may be responsive to anticholinergic drugs. Although difficulties in coordinating data in one sample and obtaining accurate data in another precluded our estimating the effect of anticholinergic drugs on post-treatment depression in our study (Galdi *et al,* 1981), we were able to provide evidence supporting anticholinergic responsiveness in a third sample (Galdi *et al,* 1982; unpublished data). This sample consisted of small numbers of genetically sub-typed schizophrenics who presented EPS (at early emergence) following routine treatment with neuroleptics. Predictably, seven patients who had depressed first-degree relatives had significantly higher depression, pseudo-Parkinsonism, and total EPS scores than four patients who had schizophrenic first-degree relatives when EPS emerged. In both subgroups, EPS responded similarly to benztropine and amantadine (a

DA agonist), although change appeared more dramatic in patients who had depressed first-degree relatives. In addition, only these latter patients showed evidence of reduced clinical symptomatology including depression after treatment. Similarly, Johnson (1981) reported orphenadrine (albeit only 100 mgs/day) to be more effective than placebo in treating post-treatment depressions, although the difference was not significant and less than half of the patients responded. However, that not all depressions respond fully to anticholinergics is not necessarily contradictory since DA-Ach balance may be involved and remission might depend on the relative potency and bioavailability of drugs antagonizing the system (Snyder *et al,* 1974).

What these preliminary findings also suggest is that difficulties exist in interpreting results from studies such as quoted by Hirsch in which anticholinergics are used in an uncontrolled fashion, and liberally, perhaps prophylactically, prescribed. Since depressions arising during neuroleptic therapy are frequently accompanied by Parkinsonian symptoms which are almost reflexively treated with anticholinergics, a reduction of depression in at least some patients would not be unexpected. By contrast, since tricyclic antidepressants may be less potent anticholinergics than the anticholinergic anti-Parkinson agents, it is doubtful that, in the presence of neuroleptic therapy, they can alleviate depressions which are neuroleptic-induced (Johnson, 1981). van Kammen *et al* (1980) recently suggested that some of these depressions may be responsive to lithium.

(5) Finally, there exist many psychometric problems inherent to measuring direction of symptom change with rating scales that should be considered in judging whether depression has been induced by neuroleptics. Depression in schizophrenics, for example, might appear (via "halo" effects) more severe during early psychotic phases than during subsequent nonpsychotic or less severe phases simply by association with greater severity, all else equal. Second, most linear rating scales are prone to "regression toward the mean" phenomena which could affect the direction of change observed, especially if depressive symptoms were initially rated more severe (high) on the scale. Third, scales vary considerably in their ability to sense change let alone its direction. In our study, for example, the semi-molecular Inpatient Multidimensional Psychiatric Scale revealed increased depression in schizophrenics with depressed heredity, while the molar Brief Psychiatric Rating Scale revealed no change or trivial decreases in these same symptoms. This difference occurred in spite of very high interscale correlations and the fact that both scales were reliably completed by the same raters in the same interviews. These selected problems imply that, since scaled ratings may not accurately reflect change in symptoms over time, issues bearing on drug-induction are probably best addressed through placebo controls and judgements of relative change. In the absence of such controls, even if neuroleptics worsened depression or impaired its remission, it might still be possible to conclude from the data that the depression just remitted more slowly (McGlashan and Carpenter, 1976b) or that it was simply unmasked (Hirsch, 1982).

A further methodological issue suggested by our own studies arises from the probable biologic-genetic heterogeneity of schizophrenia and its relationship to post-treatment depressions. If we had simply grouped all patients together, our findings would have revealed what Knights and Hirsch (1981) and others have reported: slightly decreased depression from pretreatment levels. The extent of decrease observed in any sample, moreover, might depend on the relative weighting of biologically different subgroups in the sample. The diagnostic criteria used, which might vary these weights, could also have an impact on what is observed.

What these various points seem to indicate is that depression in schizophrenia is a complex phenomenon from both methodological and theoretical perspectives. No single theory may adequately explain all of the data. Our own studies support a concept of "pharmacogenetic depression" which occurs in genetically predisposed patients as one type. In many, if not most patients, this depression is commingled with pseudo-Parkinsonism, from which it may be indistinguishable. Mild as opposed to severe expressions of this depression, however, particularly if only accompanied by akinesia, may be difficult to discriminate. Preliminary evidence suggests that it is responsive to anticholinergics and may be of nigrostriatal origin. Since it may be part of the pathophysiology of the disorder, it must also be assumed that it can occur spontaneously in the absence of neuroleptics. In our opinion, this depression may actually represent an extrapyramidal (motor) component of a DA-related disorder which often induces a subjective dysphoria that is secondary in nature (cf. Hogarty *et al,* 1979). On the other hand, I have also interviewed schizophrenic patients who are ostensibly depressed in conjunction with a severe pseudo-Parkinsonian reaction who persistently deny being depressed.

The significance of pretreatment depressions, by contrast, in the absence of diagnostic laxity, may be ambiguous. Some of these depressions may be neuroleptic-induced, persisting long after preadmission drug withdrawal, others may be purely reactive and remit with neuroleptic therapy. Findings such as Moller and von Zerssen's (1982), of initial remission of depression followed by subsequent increases in some patients,

may be difficult to explain from any viewpoint. (However, in Casey *et al* quoted above, CPZ at 400 mgs/day decreased initial depression in spite of subsequent residual effects). Obviously, additional controlled studies of these depressive phenomena are needed. In this regard, we are struck by growing reports associating depression in schizophrenia with increased risks for tardive dyskinesia. Such studies should therefore probably look prospectively at the long-term effects of neuroleptics in depressed schizophrenics.

Lest it be misunderstood, no findings to date appear to support the notion that schizophrenics predisposed to post-treatment depressions are diagnostically unique (further evaluation is indicated) nor that the use of rigorous diagnostic criteria can circumvent their occurrence (Galdi *et al*, 1981).

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2. *By Steven R. Hirsch (Department of Psychiatry, Charing Cross Hospital Medical School, London W6)*

The strength of the concept of 'revealed' depression in schizophrenia lies in its economy and simplicity. If depressive symptoms are an integral part of the schizophrenic process, these symptoms could be expected to be most frequent when the symptoms of schizophrenia are most severe, and be less prevalent as the condition remits. A post-psychotic reactive depression consequent on the return of insight, or depression which is a result of drug treatment, should get worse, not better, after treatment is commenced and not be most extant in the acute untreated phase. Numerous studies quoted by Hirsch (1981) and Galdi (1981) confirm a high prevalence of depression in acutely admitted schizophrenia, 50 per cent of cases or more. In his critique, Galdi endeavours to show how a number of factors may have contributed to this high rate of depression in acute schizophrenia yet may also be compatible with the concept of a neuroleptic-induced depression. It is important to realise that the apparent conceptual conflict between us may be more one of emphasis than flat disagreement. Our argument can be rephrased; if depressive symptoms can be proved to be most frequent during an acute exacerbation of schizophrenia and decrease after treatment begins, it is incompatible with the concept of pharmacogenic depression as the *main* explanatory hypothesis. This is not to say that the causes are not heterogeneous but only that drug-induced depression is not the main factor.

Galdi builds his argument by introducing a large number of assumptions about other researchers' data, mostly based on conjecture, which would account for a misleading high prevalence rate for depression in schizophrenia apparently independent of a neuroleptic-inducing effect. The first is "diagnostic laxity"—unlikely, given that all the studies quoted used research criteria which, though differing from centre to centre, came up with very similar results. Thus we used the PSE-CATEGO criteria of Wing, Cooper and Sartorius (1974), Johnson used the Feighner Criteria and Möller used the IMPS and the DiaSika programme. According to Möller (1981, 1982) 15–17 per cent of patients developed depression following admission, in addition to the ubiquitous 50 per cent who had depression on admission. These indeed could be drug-induced but they are a minority. In fact Johnson (1981) found a higher rate of depression among first admission untreated schizophrenics, of whom half were depressed, than among patients who had been on neuroleptics previously or at the time of admission, of whom a third were depressed. Thus the drug-induced depression concept cannot explain the higher prevalence rate of depressive symptoms found in the untreated among all acute schizophrenics. Casey's finding that depression occurred in a higher frequency in schizophrenics treated with neuroleptics until six months prior to assessment than patients never treated, and Galdi's finding (1981) that the incidence of persisting depressive symptoms was higher in schizophrenics treated with neuroleptics than those who received placebo, provided that they had a family history of depression, are as yet unreplicated isolated observations, but they would suport the existence of a neuroleptic-induced depression in schizophrenia if confirmed.

The strong association between drug-induced extrapyramidal symptoms, especially hypokinesis, muscular rigidity and loss of movement with depression (0.49–.79, Galdi, 1981) itself raises problems of interpretation. No-one has shown that depression can be reliably distinguished from pseudo-Parkinsonism with loss of movement but without depression, so the relationship may be spurious and the only drug-induced effect may be Parkinsonism, not depression. The apparent responsiveness of the symptoms to anticholinergics does not solve this problem. Johnson's assessment (1981) was based on depressive feelings and distress as well as a high Hamilton score so it would seem that his patients were depressed, in which case it remains to be determined what proportion of the patients recorded as depressed in other studies have depression, drug-induced Parkinsonism, or both.

Perhaps Galdi's most telling point about studies based on following up symptoms over time is the tendency for ratings, especially the more extreme ones, to regress to the mean. As he suggests, this can be overcome by comparing drug and placebo-treated groups, blindly rated over a time, to see if the prevalence and rating of depressive symptoms changes at different rates in the two groups. The point is to prove that a decrease noted to occur in affective symptoms over time is not an artefact inherent in repeated ratings.

Depression, as a common syndrome in acute as well as chronic patients with schizophrenia has now been revealed by numerous recent studies. As we postulated (Knights and Hirsch, 1981) causation may well prove to be heterogeneous, but as yet the most economical main hypothesis is a shared pathophysiological mechanism accounting in part for schizophrenic and depressive symptoms, and not a drug-induced one. Only further research, not polemics, can resolve this issue.

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