THEORETICAL ISSUES OF ENDOGENOUS PSYCHOSES*

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Classifications in psychiatry have always posed a challenge, particularly for those involved in the pursuit of academic systematization of syndromes (Spitzer et al., 1978). References are available which indicate that Greek Physicians developed a system which may well be termed as Biological (Nancy & Spitzer, 1979). And then we have the humoral theorists who advocated the concept of imbalances in the humours leading to the imbalance of temperaments (Fisher, 1936). This particular concept has not stood the test of time but has indeed encouraged a number of workers in the past and in recent times towards evolving a more acceptable and universal frame of reference.

We are aware of the fact that Kraepelin attempted to identify and describe definite clinical syndromes (Kraepelin, 1896). In particular he arranged mental disorders into organic psychosis, endogenous psychosis (without known structural pathology) and the deviations of personality and Reaction states. It may be recalled that endogenous psychosis was divided into two categories on the basis of phenomenological studies, i.e. Dementia Praecox and Manic Depressive Insanity. Such a division made a tremendous impact, at least at that time when confusion was the prevalent mood in terms of understanding as related to classification. We would also recall that Kleist (Kraepelin, 1921) compared the endogenous psychoses with organic states, and since there indeed were some similarities, one was left with the impression that the endogenous psychoses too were organic in nature. Kleist (Kraepelin, 1921) also made a reference to Atypical Psychoses—to which he assigned the label marginal psychosis.

In subsequent years the contributions of Kraepelin, Vernicke and Kleist either lay dormant or were inadequately highlighted. It was left to Leonhard (Leonhard, 1957-1969) to revive the interest with vigour, leading to enunciation of an impressive system of classification. Four basic types were introduced:

(i) Affective Psychosis;
(ii) Cycloid Psychosis;
(iii) Non-systematic Schizophrenia;
(iv) Systematic Schizophrenia.

Affective psychoses were further subdivided into—

(a) Bipolar type
(b) Monopolar type

Cycloid Psychoses were similarly categorized into Anxiety Blissfulness type, confusion type and motility type.

Non-systematic schizophrenias received the sub-categorization into affect-laden paraphrenia, cataphasia and Periodic catatonia. And the systematic schizophrenia included hebephrenic, paranoid and catatonic sub-types. In his system Leonhard viewed cycloid psychosis and non-systematic schizophrenia as atypical psychoses. It is thus

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abundantly clear that Leonhard's concepts are quite contrary to what is being followed at the present time.

Not only that, even more surprising is that the term endogenous psychosis does not appear in the latest edition of the well known Comprehensive Text Book of Psychiatry edited by Kaplan et al. (1980). It is a pity that the widely prevalent group of mental disorders—schizophrenias—still remains an ill-defined diagnostic category. The diagnostic criteria for Schizophrenias are as inconsistent as they are diverse (Fenton et al., 1981). In an attempt to evolve stringent nosological guidelines, the American Psychiatric Association, ended up with the emergence of a set of criteria (A. P. A., 1980), which has aroused a great deal of controversy. The applicability of the diagnostic criteria as derived through the prestigious International Pilot Study of Schizophrenia (IPSS) (W.H.O., 1973) of the World Health Organization is yet to be tested. The controversy evidently emanates from the monistic approach to schizophrenia which is in sharp contrast to the pleuristic concept of schizophrenia as originally envisioned by Eugene Bleuler (1950).

It is gratifying to observe that the pleuristic conceptualization of schizophrenias has, however, been preserved and promoted by Karl Leonhard (1979). As pointed out above, Leonhard identifies as many as 25 subtypes of schizophrenias which are divisible into two broad types—systematic and non-systematic schizophrenias. Among others, the recent pharmacotherapeutic findings (Kelwala et al., unpublished study) tend to justify the dichotomy—systematic and non-systematic—as proposed by Leonhard. It is unfortunate that Leonhard's comprehensive classification is relatively unknown outside Europe.

An added fact relating to various classificatory systems points out that specific types of psychoses are observed in almost every culture, particularly, in India (Sethi, 1978), and yet find no place in the prevalent systems of classification. For example a type of psychosis frequently associated with the abuse of cannabis (Bhang) has been identified in India (Verma, 1972; Thacore, 1973; Chopra and Smith, 1974). While the clinical picture of cannabis psychosis shares many symptoms of paranoid schizophrenia, the two types of psychoses are quite distinct from each other (Thacore and Shukla, 1974).

Briefly one may note that cannabis use in India is quite common. Prolonged, perpetual or even an occasional use of cannabis may produce psychiatric illness of intense proportions. There is a vast literature on the subject, especially from countries like India, Egypt, Morocco and Nigeria (Baselqu, 1972). Some workers contend that cannabis in itself does not have the capacity to produce psychiatric illness, though it might precipitate such an illness in those who are predisposed. In contrast some workers (Varma, 1972; Thacore 1973; Chopra & Smith, 1974) have described conditions known as 'Cannabis Psychosis' or 'Bhang Psychosis'. However the existence of the entity remains controversial. However, the description of the syndrome is considered as being far from clear—especially when it is taken into account that symptoms said to be characteristic of the state are also common to other toxic states, including those associated with malnutrition and infections. In early studies (Kolansky and Moore, 1971; Halikas et al., 1971)—no specific association between cannabis and psychosis was noted. However, (1974) and (Agarwal et al. (1975) revived the concept and described cases with features such as—temporal association with cannabis intake, bizarre or aggressive behaviour, elation with increased flow of thought but no schizophrenic thought disorder. It is characterised by complete recovery. It should however be different
tiated from paranoid schizophrenias.

A general consensus seems to be that cannabis might precipitate a state of psychosis particularly in those who find it difficult to manage anxiety. And possibly because of this controversy cannabis psychosis is not listed in ICD-9.

The term Hysterical Psychosis (Wig and Narang, 1969) though in use for a long time is also not a part of ICD-9 or DSM-III. In the latter it is listed under Brief Reactive Psychosis. The main clinical features are a recognizable stressful event preceding appearance of symptoms, emotional turmoil characterized by incoherence, markedly illogical talks, delusions, hallucinations, markedly bizarre behaviour and volatile affect. It may last from a few hours to a few days. The patients have a poor insight. By definition the main precipitating factor is a major stress experience, closely related in time to emergence of symptoms. Unstable personalities seem to be much prone to develop hysterical psychosis. There are till date no genetic links demonstrable but the disorder is not considered as one of the spectrum disorders of schizophrenia (Rosenthal and Kety, 1978).

In the Bleulerian sense of schizophrenias, as also shared, in particular, by Leonhard (1979), both, cannabis and hysterical psychoses may be conceptualized as only two of the myriad forms of schizophrenias. It might therefore, seem unwise to label these and other related forms of psychoses as atypical psychotic disorders, a classification which is followed just because of custom and convenience. The concept that the schizophrenias represent a syndrome with different underlying pathological process is substantiated by the recent biochemical findings which tend to differentiate one from the another subtype of schizophrenias (Wyett et al., 1980).

After comparing diagnostic criteria, as proposed by Knight (1953), Kernberg (1967), Grinker et al. (1968), Gunderson and Singer (1975) and Perry and Klerman (1978) were obliged to consider the borderline concept as an illusion. While the borderline patients continue to be identified (Kroll et al., 1982) the very concept of this disorder is undergoing radical revisions. Recently, Stone (1979) has traced the contemporary shift of the borderline concept from a sub-schizophrenic disorder to a subaffective disorder. It cannot be over-emphasized that the borderline states have not only defied the definition but also proved to be a therapeutic challenge. Therefore, this area of research deserves particular attention.

Perhaps because of a strong psychoanalytical and psychodynamic trends/forces, the organic aetiology as conceived by Kraepelin (1896), Wernicke, Kleist, and Leonhard (1957, 1969) did not receive an appropriately justifiable attention. And compatible with the syndromal and pleuristic view of schizophrenias will be the reasoning that there may be more than one etiological basis of the development of schizophrenias. A variety of etiological theories including an autoimmune theory (Solomon, 1981) of schizophrenias have been proposed. I should like to comment at length on this model, which appears to be based on some interesting observations.

The roles of thymus, T-lymphocytes and immunoglobulins in the regulation of immune function remain undisputed. There is some evidence that the patients of schizophrenia (Fessel and Hirata-Hibi, 1963; Fowle, 1968) and their family members (Sethi et al., 1973) show morphologic abnormalities in lymphocytes.

In a study conducted in 1971 in our department (Sethi et al., 1973) a relationship was studied between presence of atypical lymphocytes and psychiatric disorders. It
was pointed out that all schizophrenics studied in the series demonstrated atypical cells. A much lesser frequency of these atypicals was also observed in depressive and psychophysiological disorders. A subsequent study (Sethi and Sethi, 1971) was completed in 1973. A genetic influence producing a specific cellular response to stress which in schizophrenic patients assumes a different variety as compared to controls and other psychiatric syndromes was considered as a possibility.

Recently, certain functional changes in lymphocytes of untreated schizophrenic patients have been demonstrated (Vartanian et al., 1978). The latter findings are extremely important since similar changes have also been shown to be caused by phenothiazines (Boker et al., 1977). The question of neuroleptic-induced atypical lymphocytes was specifically addressed in a very recent investigation which indicated that the neuroleptics did not seem to influence the occurrence of atypical lymphocytes (Hirata-Hibi et al., 1982). The whole area of research pertaining to the morphological and functional changes in the lymphocytes of patients with schizophrenia is so exciting that it certainly deserves further explorations, as also emphasized by Solomon (1981).

The repercussions of the lymphocytic abnormalities may be observed in the quantitative and qualitative variations of serum proteins, particularly immunoglobulins. There are large number of reports on changes in the level of γ-globulins and their fractions in patients with schizophrenia (Tomey et al., 1976; Prakash and Sethi, 1978).

In a study (Tewari, 1981) carried out in our department and currently in press it was decided to study the pattern of immunoglobulins and viral antibodies in serum and CSF of schizophrenics and depressive subjects, and to determine relationship between duration and episode of illness and immunoglobulin level and antibody titre.

The results of the study revealed that in depressives (33.6%) and neurological controls (45%) total CSF protein was increased while there was no increase in schizophrenic patients. High mean serum values of Ig G were observed in depressives and neurological controls as compared to surgical controls, and mean serum value of IgA was higher in schizophrenics, depressives and neurological controls as compared to surgical controls. Mean value of CSF IgG/ total protein % (T.P.) was high in schizophrenics, depressives and neurological patients as compared to surgical controls. CSF IgA was detected in depressives and neurological controls but not in schizophrenic and surgical patients. The findings of antibrain antibodies and HLA antigens specific to schizophrenias (Baron et al., 1977; Pandey et al., 1981) are compatible with the autoimmune theory of schizophrenias but are inconclusive.

The identification of endorphins (Hughes et al., 1975) endogenous morphinomimetic substances and their implications in psychotic disorders forms perhaps the most significant research of the past decade. A gross inconsistency of the data is equally true about the research in this area. The controversy is evidenced by the findings which suggest an excess of endorphins (Terenius et al., 1976; Lindstrom et al., 1978; Limon et al., 1980), a deficiency of endorphins (Kline et al., 1977; Lehman et al., 1979) and a poor availability of a particular fraction (γ-type) of endorphins in patients with schizophrenias (Verhoeven et al., 1979; 1978; Van Praag et al., 1982). The literature has been recently reviewed by Van Ree et al., (1981). The original and perhaps the most popular view excess of endorphine has been questioned lately on the basis of clinical trials (Gunne et al., 1977; Davis et al., 1977; Janowsky et al., 1977; Kurland et al., 1977; Emrich et al., 1978; Watson et al., 1978), using an opiate-antagonist. The findings have been
discussed elsewhere. However, it is worth noting that due to differential affinity of the opiate receptors, antagonists such as naloxone may not be the appropriate agents for delineating various central roles of enkephalins (Mackay, 1979). Because the morphinomimetic substances have been recently found to interact with the dopaminergic system (van and Wolterink, 1981) and because beta endorphins are converted into \( \gamma \) endorphins (Burbach et al., 1980) further investigations must be undertaken to gain insights into the etiological roles of \( \beta \) and \( \gamma \) endorphins in schizophrenia. Such investigations are further justified by the encouraging therapeutic results with beta endorphins and \text{Des-Tyr}^1-\gamma \text{endorphin} (Veheoven et al., 1978; 1979; Van Praag et al., 1982).

Aetiology therefore of disorders to be included in the Endogenous Psychosis group remains an enigma of no small magnitude. A number of crucial leads are now available, any of which may be holding the key for the future. Genetic, biochemical, the psychodynamic and the social aspects have been emphasized from time to time. Of late, however only the genetic and the biological theories are receiving the long awaited attention. It is worth noting that as a result of genetic studies of affective disorders presented a system of diagnosis in unipolar depression. Winokur and Clayton (1969) coined the two subcategories: (i) depression spectrum disease in which a first degree relative has alcoholism or antisocial personality or both and (ii) pure depressive disease in which a first degree relative have history of depression. These nosological categories which though do not find a place in standard official American Psychiatric Association or WHO classification, have been supported by distinct genetic, phenomenological and outcome features. Their exact nature will be clear only in the years to come and with more studies (Winokur and Tanna, 1969).

Leonhard (1957—1969) also described atypical schizophrenias which he called non-systematic schizophrenias and differentiated from systemic schizophrenias (typical) on the basis of phenomenological studies and later he proved their independent existence on the basis of genetic studies in which he found that the rate of genetic transmission is much higher and prognosis poorer. Though these atypical entities of typical endogenous psychosis have recently created interest in other workers too, it still remains a poorly studied one (Fish, 1964).

Currently high risk longitudinal studies are in progress in vulnerable subjects. On the basis of expectancy rates in genetic family studies, the children of one schizophrenic parent (with 10-15% risk) and of two schizophrenic parents (with a 40% risk), are being studied from early years and researchers hope to identify preexisting biochemical, psychophysiological, neurological, behavioural and environmental characteristics that might differentiate those who become schizophrenic from those who do not (Van Parag, 1981). A similar strategy is also required for affective psychosis to solve the genetic riddle, where again prospective studies would be more valuable.

Treatment

Undoubtedly, the neuroleptics remain the drugs of choice in the treatment of schizophrenia. However, various reasons, including the recent identification of a syndrome (Gardos and Cole, 1980) of tardive dyskinesia in patients receiving neuroleptics have promoted the exploration of alternative therapeutic agents. We should like to briefly review the therapeutic results with lithium, opiate-antagonists as well as endorphins and beta-adrenergic blocking drugs.

Lithium

The previous investigations have not
only reported a lack of therapeutic response with lithium in schizophrenics but also a development of neurotoxicity (Shopsin et al, 1971). While encouraging results had been obtained with lithium in individual cases of schizophrenia, the research received a fresh impetus after the publication of a study in 1975 (Small et al, 1975). The investigators boldly employed a combination of lithium and neuroleptics with success in spite of the fact that a similar therapeutic strategy had been found to induce neurotoxicity (Cohen and Cohen, 1974). A score of investigations have since been undertaken with variable success (Alexander et al, 1979; Biederman et al, 1979; Growe et al, 1979). The antischizophrenic potential was also explored in a double-blind investigation at our center (Dube and Sethi, 1981). A total of 60 inpatients carrying a diagnosis of schizophrenia received lithium or chlorpromazine. The 4-week period of active medication was preceded and followed by placebo therapy. While, generally speaking, chlorpromazine was superior to lithium, the latter produced beneficial effects on several core symptoms—emotional withdrawal, conceptual disorganization, suspiciousness, ideas of persecution and passivity and nonspecific symptoms of schizophrenia—somatic concern, motor retardation, impaired concentration, excitement, hostility and anxiety. There was no evidence of predisposition for neurotoxicity in patients receiving lithium.

In another unpublished study (Dube, 1980) an evaluation of the antischizophrenic effects of lithium-neuroleptic combination in 24 patients who had shown only minimal response with neuroleptics was completed. The patients were classified according to Leonhard’s criteria. The investigators concluded that lithium-neuroleptic combination was effective in unsystematic schizophrenias and not only ineffective in systematic schizophrenias but also neurotoxic. While these findings await replication in controlled investigations, they do indicate a therapeutic role of lithium in disorders characterised by a phasic course as the latter has been described as a cardinal feature of unsystematic schizophrenias. The inference is lent support by investigations which have reported favourable results with lithium in schizo-affective disorders (Alexander et al, 1979; Biederman et al, 1979) also characterised by a phasic course. Our positive data together with those reported in the literature would caution against the premature labelling of lithium as exclusively antimanic agent.

Our present understanding of neuroanatomy, neurophysiology neurotransmitters, neurohormones and psychoneuropharmacology have opened up new channels in the field of endogenous psychoses. The mono-amine hypothesis of schizophrenia implicating neurotransmitter dopamine (Carlsson and Lindquist, 1963), monoamine oxidase (Murphy and Wyatt, 1972) and aberrant o-methylation of catecholamines (Osmond and Smythies, 1952; Domino and Gahagan, 1977; Wyatt et al, 1973) and GABA (Roberts, 1972) involvement has been on one hand supported and on other hand refuted, leaving the whole situation in a dilemma. More recently endorphins (Sethi and Prakash, 1981) have been implicated in schizophrenia. This particular hypothesis is being tested by the WHO in an International Collaborative Study by using Naloxone as an opiate antagonist (Verhoeven et al, 1981). Another recent development is the role of Beta adrenergic antagonist propranolol (Schulz et al, 1980) in schizophrenia. These recent developments have undoubtedly made a significant advancement in the treatment of schizophrenia but the nature of illness still remains unresolved, though considerable understanding has emerged.

Opiate Antagonists and Endorphins

The theoretical justification for the use
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of opiate antagonists and endorphins in the treatment of schizophrenia has been discussed elsewhere. The theory that schizophrenias are characterised by an excess of endorphins has been clinically tested in a score of positive (Gunne et al, 1977; Emrich et al, 1978; Watson et al, 1978) and negative (Volavka et al, 1979; Kurland et al, 1977) studies. It was tested in a prestigious multicenter investigation sponsored by the World Health Organization. The investigation included patients with schizophrenia and mania. The results are now available (Sethi and Prakash, 1981). At our centre in a study of 11 patients with schizophrenias who subcutaneously received 0.3 mg/Kg of naloxone or placebo, we did not observe any significant change in the psychopathology upto 6 hours after the medication (Verhoeven et al, 1981).

The theory of deficiency of endorphins is related to the observations of therapeutic success with administration of Beta endorphin (Kline et al, 1977; Lehman et al, 1979). It is likely that Beta endorphin-induced improvement in schizophrenia is related to an inherent neuroleptic potential because Beta endorphin (Schulz et al, 1980) as also other neuroleptics (Meltzer and Fang, 1976) have been found to elevate prolactin levels. The notion is in fact supported by the observation that Beta endorphins are converted, in brain, into (Des-Tyr

Beta Adrenoceptor Blocking Drugs

The identification of antipsychotic potential of beta adrenoceptor blocking drugs was quite a serendipitous discovery (Atsmon and Blum, 1970). A score of positive (Atsmon et al, 1972; Yorkston et al, 1974; 1981; 1977; Sheppard, 1979) and negative (Gardos et al, 1973; King et al, 1980; Peet et al, 1981) studies have since been reported. An inconsistency of data has been attributed to various factors—differences in research designs, selection of diagnostically heterogenous group of patients, differences in the dose of drug, and conjoint medication with neuroleptics and beta blockers (Prakash and Sethi, unpublished data). The last factor has assumed particular importance due to recent revelations of pharmacokinetic interactions between the two classes of drugs (Peet et al, 1981). Propranolol has been found to cause ele-
vation of plasma levels of neuroleptics, thereby reducing the dose requirement of the latter. The foregoing interactions and effects, if maintained over a period of time may minimize the risk of the development of tardive dyskinesia.

It may be of interest to note that we took schizophrenic inpatients (Sethi and Dube, 1981) who fulfilled the standard inclusion and exclusion criteria and administered propranolol after a complete assessment of physical status. The drug was given for 4 weeks according to the following regimen:

- Day 1–6 .... 160 mg/day
- Day 7–9 .... 480 mg/day
- Day 10–12 .... 960 mg/day
- Day 13–16 .... 1600 mg/day
- Day 17–28 .... 1920 mg/day

Patients whose pulse rate fell below 55/mt and b.p. below 80/50 mm of Hg. were dropped from the study. Weekly ratings of total scores of MBPRS recorded highly significant (p<0.001) improvements in scores of weeks 2 and 4 when compared to the baseline and among themselves similar level of improvement was seen on the CPRS scores of weeks 2, 3 and 4 when compared to the baseline scores and those of week 1. The improvement beyond week 3 was significant at 1% level only (Mann Whitney-U-test). Using the students test, 8 items of MBPRS showed a highly significant improvement (P<0.001) at the end of 2 weeks and maintained till the end of the study. On the CPRS subscale, 13 out of 39 items showed an improvement at 5% level after 2 weeks of active treatment. During the 3rd and 4 weeks highly significant improvements (p<0.01) were seen on the 7 items. Only 3 patients were dropped due to severe CVS effects. Most side effects when severe occurred during the first 72 hours of therapy and Beta blocking effects were not related to clinical improvement. Our observation is that the drug possesses antipsychotic properties and is safe. Double blind studies are recommended for further exploring this lead.

CONCLUSIONS AND RECOMMENDATIONS

1. Schizophrenias represent a heterogeneous group of disorders. With few exceptions, the available classificatory systems do not seek to minutely and clearly discern various subtypes of schizophrenias. Certain culture-related forms of psychoses have to be classified as atypical disorders for want of specific diagnostic categories. Also, the issue of borderline psychoses remains unresolved. The nosological problems appear to be related to exclusion of pleuristatic approach to schizophrenias, as originally envisioned by Eugene Bleuler. Further expansion of the available diagnostic systems, along the lines of Leonhard, must be done.

2. A heterogeneous group of disorders cannot be conceived to have just one etiological basis and one therapeutic answer. The theories linking immunological changes and changes in the endorphin systems with schizophrenias are two of the various etiological models of schizophrenias. Morphological and functional patterns in lymphocytes of patients with schizophrenias appear to be immensely significant and need further explorations.

In the area of endorphin research, further investigations with beta-endorphins and (Des-Tyr^1)-endorphin must be undertaken in patients with schizophrenias. Lithium and beta adrenoceptor-blocking drugs constitute a good treatment in addition to neuroleptics, if not alone in their own right. There is, however, some need for the identification of individual subtypes of schizophrenias which respond to different therapeutic strategies. A multi-centre study of atypical psychoses with particular attention to genetic, neuro humoral, psychopharmacological and pharmacological aspects should be of help in clarifying a variety of issues raised.

Lastly we wish to emphasize that Biologi-
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Cal Psychiatry now provides an excellent scientific base of knowledge, methodology and clinical applicability. But more is required to be studied in order to clarify several issues involved in endogenous psychoses. A major research work is being done in advanced countries—especially the affluent ones. In developing countries there is paucity of research work and information. Two major factors hampering research work are: (a) lack of facilities for research training and (b) lack of facilities and resources for research (Sethi, 1980). The problem in setting up biological research for endogenous psychoses in India would arise from various sources. Lack of manpower, financial unavailability, lack of well equipped laboratories, limited familiarity with research methods, and inadequate transfer of information are the outstanding problems prone to affect research work. Malnutrition, illiteracy, cultural beliefs, and lack of sponsorship may be other factors likely to affect research work (Sethi and Sharma, 1981).

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