

## CHRONIC SCHIZOPHRENIA—A PSYCHOPHARMACOLOGICAL APPROACH<sup>1</sup>

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### SUMMARY

Our work suggests that the Leonhard classification system holds much promise as a framework for future nosological development. One might speculate along biochemical lines that the nonsystematic subpopulation of schizophrenics may suffer from altered dopamine  $\beta$ -hydroxylase activity which results in an excess of dopamine. This would explain why this class responds so well to dopamine receptor blocking agents when other patients do not.

One might also speculate that we are dealing with a number of diseases—each with different courses and progressing to different end states, but all with common pattern during the acute stage, *e. g.*, increased dopamine levels or receptor sensitivity levels. This is probably why the acute stage can usually be controlled by the administration of a dopamine receptor blocking agent.

A further speculation concerns the catatonic patient who had begun to respond to psychosocial and milieu treatment prior to the introduction of neuroleptics. This particular group of patients do not seem to benefit from prophylactic treatment with neuroleptics. If, by activating a patient, catecholamines are released, it is hypothesized that the catatonics are a completely separate subpopulation—not just clinically—but also biochemically.

Completely different types of drugs may be helpful for the different schizophrenic subpopulations. Among the various substances, propranolol should be considered. Obviously, this drug will not be effective in all schizophrenics; but there are certain types of patients who respond to  $\beta$ -blockers. There is also increasing evidence that clonidine (which stimulates alpha-adrenergic receptors) may also have an effect on certain schizophrenics. The most recent findings is that cholecystokinin—thought for some time to be an exclusively peripheral substance—appears to be present in the brain and available in the form of ceruletide, a neuropeptide which is a dopamine agonist. This substance, also, seems to be effective in the treatment of certain schizophrenics.

Chronic schizophrenia requires re-evaluation and it should be recognized that different drugs are effective in different types of patients. There is renewed interest in the various schizophrenic conditions and their end states. We must hope that the pharmacologists, provided with sufficient information, will search for new drugs with differentiated activities that will meaningfully influence the end states of schizophrenic disorders and/or prevent their development.

That at least one person in 150 is affected by schizophrenia is a familiar statistic. Less well known is the fact that 15% of those so diagnosed become chronically hospitalized—a percentage more or less applicable everywhere in the world. Another often unrecognized fact is that only 50% of the schizophrenic population benefit definitely from long-term neuro-

leptic treatment. While a considerably higher proportion may, at one time or another, respond favorably to neuroleptics, only 50% appear to receive definite benefit from the administration of neuroleptics on a prophylactic basis.

Neuroleptics are the primary mode of treatment for schizophrenia today. However, it must be recognized that

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neuroleptic therapy cannot prevent the development of the various end states of schizophrenia, although it can modify the course of the illness and control an acute episode or an exacerbation. Furthermore, it must also be remembered that the use of neuroleptics is not without its risks. As with any potent treatment, there is a price to pay for the therapeutic benefits. Long-term administration of neuroleptics can have serious adverse side-effects. One can appreciate the benefits of neuroleptics, but it is important to keep in mind that a patient treated with these drugs on a long-term basis may exhibit certain neurological changes, e.g., tardive dyskinesia. Given that only 50% of schizophrenics benefit from long-term treatment, this potential risk must be of concern to all treating physicians.

#### THE LEONHARD CLASSIFICATION

Traditional psychiatric thought on chronic schizophrenia is based on principles elaborated by Kraepelin (1896) who, with considerations to Kahlbaum's (1876) contributions, introduced the time component to psychiatry, i.e., that the understanding of the course of an illness is essential for proper diagnosis. A second principle was introduced by Bleuler (1950) who described the immediate picture of the disease by a careful elaboration of its psychopathological symptoms.

Wernicke (1906), a contemporary of Kraepelin found that diagnosis was especially difficult in the acute stage of a psychiatric illness and recognized that, almost regardless of what happens during schizophrenia's course, the illness finally crystallizes into some type of stable end state. It may be five or six years after an acute episode has subsided before an accurate psychiatric diagnosis can be made. This, therefore, shifted the emphasis from the acute to the chronic end state of the illness.

Leonhard, a disciple of Wernicke and Kleist, continued to emphasize the importance of end states (Leonhard, 1979). He added a third component to the concept: the polarity of the illness. Like affective psychoses, the schizophrenias for Leonhard encompass both bipolar and unipolar illnesses. The bipolar illnesses are called nonsystematic schizophrenias. They are characterized by their intermittent periodicity, their partial resemblance to manic-depressive disorder and their relatively good prognosis. The unipolar schizophrenic illnesses are labelled systematic. Systematic schizophrenias have a downhill course greatly resembling that of the organic dementias, except that they feature intermissions that never quite reach full remission.

Further, within these two classes (systematic and nonsystematic) small subpopulations can be discerned by considering the three crucial components of psychiatric diagnosis: psychopathological symptoms, behavior and performance. These three components are not always uniformly impaired. Some patients may exhibit very severe psychopathological symptoms but have a virtually intact performance. Others may have badly impaired performance but manifest minimal psychopathology.

There is, for example, one type of paraphrenia (phonemic) in which performance remains virtually intact despite the fact that patient is almost permanently under the influence of auditory hallucinations. There are hebephrenic patients who are almost totally autistic but, with prompting and in the right kind of environment, may perform exceptionally well on routine tasks. Within the catatonias, the most severe form of schizophrenia, there is a subtype, the parakinetic, which displays relatively good performance.

Leonhard recognized the existence

of these dissociations in the end-states and employed them in his conceptualization of the schizophrenias. He identified three subgroups within the nonsystematic class: affect-laden paraphrenia, cataphasia and periodic catatonia. He also described three sub-groups within the systematic class: paraphrenias, hebephrenias and catatonias. Finally, Leonhard subdivided the paraphrenias into six subtypes, the hebephrenias into four and catatonias into another six.

Leonhard conceives the schizophrenias as dissociations among the perceptual (cognitive), emotional (affective) and motor (adaptive) systems. An acute episode is characterized by a dissociation among these systems leading to a "step-backwards" in one of the systems. Although the term "regression" has been contaminated by its use in psychodynamics and in many other contexts, what one sees in all these different schizophrenic subtypes are different dosages of regression in the cognitive, affective or adaptive system.

#### LEONHARD SUBTYPES AND RESPONSIVENESS TO DRUGS

Questions are frequently raised concerning the generality and clinical relevance of the Leonhard classification system. Wilson and Ban (1983) compared two distinct populations which have been so classified: 664 patients classified by Leonhard (1936) prior to the psychopharmacological era and 900 patients classified by Astrup (1979) after the advent of psychotropic drugs. A very high correlation was obtained between the two cohorts: the distribution and rank order of the Leonhardian subtypes had not changed from the pre-to the post-psychopharmacological era.

Also of major importance was the work by Hamilton (1962) which demonstrated clearly that responsiveness to

different psychotropic drugs varied among the different schizophrenic subtypes. He was able to demonstrate quite convincingly that 95% of the nonsystematic schizophrenics showed moderate to marked therapeutic responsiveness to neuroleptics. In contrast, a much lower percentage of systematic schizophrenics reached similar levels of responsiveness to neuroleptics.

Fish also brought to attention that, in the most responsive treatment group of systematic schizophrenics—the paraphrenics—therapeutic responsiveness in the chronic phase of treatment was less than 50%. During the same phase catatonics proved virtually unresponsive to neuroleptics. Responsiveness here refers to maintenance and prophylaxis—not acute treatment. Maintenance refers to treatment of the patient up to the expected end of the acute episode and prophylaxis refers to treatment beyond that time, i.e., the prevention of a further episode.

Kelwala and Ban (1981a) described a patient who had been diagnosed as suffering from febrile catatonia. When the patient became feverish, he developed delusional ideas, waxy flexibility and mutism. He was initially treated with haloperidol and later chlorpromazine was added—neither with any appreciable effect even when the dosage was increased. It was decided to reduce his medication by discontinuing the chlorpromazine and lowering the dosage of the haloperidol. As a result the patient improved sufficiently enough to go home for a week. There was further improvement at home and deterioration upon return to hospital. At this point, it was determined that he was not taking his medication while at home. Since patient seems to fair better without drugs, treatment with neuroleptics was discontinued altogether. Discontinuation of medication was followed by remission

of psychopathological symptoms. It was concluded that this patient not only had a poor response to neuroleptics; but that he may have had a negative response.

Two other examples involved patients who were classified in Leonhard's system as shallow hebephrenics (Kelwala and Ban, 1981b). Their prevailing characteristics were flatness of affect, lack of interest and total lack of spontaneity. Both were admitted to hospital because they experienced sudden, episodic, hallucinatory excitements during which they would strike someone or otherwise create a disturbance. One patient was treated with thiothixene, the other with haloperidol. However, when their medications were discontinued, no changes were observed in their behavior (i.e., their episodic outbursts remained at about the same frequency whether given neuroleptics or not). Although there are indications that this particular schizophrenic subtype might be responsive to carbamazepine, in these patients carbamazepine remained ineffective. There is, therefore, a second chronic schizophrenic subtype which responds only minimally to neuroleptics and consequently does not necessarily benefit from prophylactic treatment with these drugs.

#### RECENT WORK

We are currently carrying out work in relation to Leonhard's classification. Preliminary data show that not only is there different responsiveness to neuroleptics among the schizophrenic subpopulations but that these differences may be intuitively perceived by psychiatrists who prescribe different dosages of neuroleptics for what turn out to be specific Leonhard subtype. It appears that the nonsystematic class receive significantly higher dosages than the systematic class. This is important because the nonsystematic class seems to be a genetically distinct schizo-

phrenic subpopulation with a relatively good prognosis. Among the systematic schizophrenics, it was found that the paraphrenics were receiving significantly higher neuroleptic dosages than the hebephrenics and catatonics. This may be because neither of the latter two subgroups exhibit much response to neuroleptics in chronic treatment.

Another interesting observation is that tardive dyskinesia seems to occur three times more frequently in the chronic disorganized population, i.e., those patients usually falling into the hebephrenic and catatonic subgroups, than in the paraphrenic subgroup. Tardive dyskinesia was rarely found among nonsystematic schizophrenics. It is worth considering whether tardive dyskinesia only manifests itself in those subgroups which do not benefit from prophylactic treatment with neuroleptics and which should not have been placed on maintenance or prophylactic therapy in the first place.

Also of interest were the data that emerged in relation to lithium. As we have been working with chronic patients, everything possible including lithium, had been tried in order to help them. Although we expected little from this treatment, it was found that, among patients on combined lithium-neuroleptic therapy, nine out of 10 nonsystematic schizophrenics (mainly affect-laden paraphrenics) showed a favorable therapeutic response and none developed a toxic confusional state. In contrast, a considerable proportion of systematic schizophrenics developed a toxic confusional state to the combination (Prakash et al., 1982).

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