Thomas A. Ban: Neuropsychopharmacology in Historical Perspective
Psychopharmacology and the Classification of Functional Psychoses

11. Schizophrenic Psychoses

From Dementia Praecox to Schizophrenia

The first clinical description of patients who were to be diagnosed later as schizophrenic was in Morel's (1853) *Etude Cliniques* in which he described "young mental patients" with a particular kind of sudden degeneration. Yet, it was only seven years later in 1860 (in his *Traite, des Maladies Mentales*) that he termed this "sudden immobilization of all the faculties" as *demence precoce*."

The concept of *demence precoce* remained dormant until Kraepelin (1893), in the 4th edition of his textbook, brought together the syndromes of hebephrenia, described by Hecker (1871), catatonia, or tension insanity described by Kahlbaum (1874), and *dementia paranoides* that was singled out by him from the vast range of paranoias, under the heading of "psychological degeneration processes."

Subsequently, in the 5th edition (1896) he characterized this "group of clinical conditions" by its "peculiar destruction of internal connections of the personality and a marked damage of emotional life." As patients who belonged to this group of illness showed considerable resemblance to what Morel (1852, 1860) described under the term *demence prec*oce, Kraepelin adapted the term *dementia praecox* and used it three years later, in 1899, to designate a single disease progressing towards "psychic enfeeblement" that manifests in three forms: hebephrenic, catatonic and paranoid.

In the 7th edition (1904) of the textbook, the paranoid type of *dementia praecox* embraced Magnan's (1893) *delire chronique*.

In the 8th edition (1909-1915), a distinction was made between the paranoid form of *dementia praecox* proper and other "paranoid deteriorations" referred to as "paraphrenias" (Pichot

1983). In the paraphrenias, in contradistinction to *dementia praecox* disorders of emotion and volition, even if present, are not marked. To comply with the new definition, *delire chronique* was transferred to the paraphrenias (Pichot 1983). For Kraepelin this separation remained valid on clinical grounds. It was Mayer (1921) who later subsumed paraphrenias under the schizophrenias.

Thus, in the 8th edition of his textbook, Kraepelin put forward a completely different subdivision of the group of disorders he subsumed under *dementia praecox*. The new "classification" distinguished among 10 different forms: dementia simplex, silly deterioration (*lappische verblodung*), depressive deterioration, depressive deterioration with delusional formations, circular forms, agitated form, periodic form, catatonia, paranoid form and schizophasia. It was also in the 8th edition that Diem's (1903) concept of "dementia simplex" was adapted and in which the term "silly deterioration" was substituted for "hebephrenia."

The changes proposed in the 8th edition remained isolated from the main stream of psychiatry. Instead, it is the classification from the 5th edition which distinguishes three forms – hebephrenic, catatonic and paranoid – that is usually referred to as Kraepelin's.

Kraepelin's classification was operationalized several decades later, in 1982, by Landmark (1982).

By replacing Kraepelin's nosological hypothesis with a pathogenetic one and the term *dementia praecox* with the term "schizophrenia," Eugen Bleuler (1911) confirmed and consolidated the concept. He defined schizophrenias as a "group of psychoses" characterized "by a specific type of thinking, feeling and relation to the external world" which "appears in no other disease in this particular fashion." Accordingly, Bleuler distinguished between "fundamental" and "accessory" symptoms of schizophrenia. He also asserted that the fundamental symptoms, i.e., loosening of associations, inappropriateness of affect, ambivalence and autism (referred to as the four-A's), are exclusive to schizophrenia, whereas the accessory symptoms occur in other psychiatric conditions as well. Bleuler also distinguished the "primary symptoms of schizophrenia" from the "fundamental symptoms" and considered the "primary symptoms," such as disturbance of associations, affective changes (possibly), hallucinations (possibly), stereotypes and physical disorders (such as vasomotor and pupillary changes) – direct expressions of the brain disease – whereas the secondary symptoms were derived from the primary pathological phenomena. With consideration to "fundamental" and "accessory," as well as "primary" and "secondary" symptoms, Bleuler distinguished among four types of

schizophrenia: simple, paranoid, hebephrenic and catatonic.

In the DAS, based on the DCR (Pethö, Ban, Kelemen et al. 1984), substantiation of the diagnosis of schizophrenia is based on the evaluation of 10 variables. The variables include symptoms which can be present in any psychosis (delusions, hallucinations) and variables which are specific to schizophrenia, such as catathymic evolvement of symptoms and dissociation among perceptual – cognitive, relational – affective and motor-adaptive functions (split). The other variables include formal thought disorder that disturbs comprehensibility (primary incoherence, tangential thinking, blocking, derailment, desultory thinking and/or onematopoesis), affective changes (blunted, inadequate and/or inappropriate) and personality changes (abandonment of habits, change in life style, incomprehensibility of behavior and/or autistic behavior). Additional prerequisites are clear consciousness, the absence of holothymic evaluations and the consistent presence of psychopathology.

Diagnoses corresponding to schizophrenic psychoses in the DCR are labeled as schizophrenic psychoses in ICD-9 and schizophrenic disorders and schizophreniform disorders in DSM-III.

In ICD-9 the diagnosis of schizophrenic psychoses is not restricted to disorders running a protracted, deteriorating or chronic course. In contradistinction to the DAS criteria, in ICD-9 considerable emphasis is placed on disorders of the ego, such as the sense of being controlled by alien forces and that one's thoughts, feelings and acts are known to or shared by others. There is also greater emphasis placed on explanatory delusions, e.g., that natural or supernatural forces are at work and responsible for patient's clinical state.

DSM-III criteria of schizophrenic disorders correspond also with DAS criteria. In certain respects, however, the diagnosis is restricted in that the illness needs to occur before age 45 and continuous signs of the disorder must be present for at least six months. When the duration of illness is longer than two weeks but shorter than six months, the diagnosis in DSM-III is schizophreniform disorder.

In spite of its high, almost 1% prevalence rate in the general population – and the recognition that the lifetime risk for children of schizophrenics is approximately 15 times higher than that of the 0.86% in the general population – there are no generally accepted criteria for the diagnosis of schizophrenia (Tsuang and Vandenney 1980). The most frequently employed clinical and/or research criteria were summarized by Berner, Gabriel, Katschnig et al. (1983) in *Diagnostic*

Criteria for Schizophrenic and Affective Psychoses. They included Schneider's (1957) First Rank Symptoms, the *St. Louis Criteria* (Feighner, Robins, Guze et al. 1972), the *New Haven Schizophrenia Index* (Astrachan, Harrow, Adler et al. 1972) the *Flexible System for the Diagnosis of Schizophrenia* (Carpenter, Strauss and Bartko 1973), the *Present State Examination Criteria* (Spitzer, Endicott and Robins 1978a,b), *Taylor and Abrams Criteria* (Taylor and Abrams 1978; Taylor, Redfield and Abrams 1981), and the VRC (Berner and Katschnig 1983). In view of the difficulties encountered in identifying generally acceptable criteria for the diagnosis of schizophrenia and contributions of recent investigations, especially by Koehler (1979), and Berner (1982), it has been suggested that schizophrenic symptoms have "no differential diagnostic weight for distinguishing between schizophrenia and cyclothymia" (referring to affective psychoses) (Berner, Gabriel, Katschnig et al. 1983).

From Schizophrenia to the Schizophrenias

The first information on the natural course of schizophrenia dates back to Kraepelin (1899, 1919) who described *dementia praecox* as a disease which, as a rule, is progressive particularly with regard to emotional deterioration even if in a few cases the process may come to a standstill and symptoms may remit, disappear. Kraepelin's figures for a group of inpatients diagnosed as *dementia praecox* at the Heidelberg Hospital showed that of the 12.6% who had a complete remission first, 8.5% relapsed three to six years later and only 4.1% remained well. The figure of 12.6% could be raised to 13.3% by adding to it all the cases with only a mild defect and to 17% by extending it to all the cases that would live a more or less socially adjusted life independent of the degree of defect (Hoenig 1967). It was noted that 70% of Kraepelin's *dementia praecox* patients severely (deeply) deteriorated.

The three crucial figures of Kraepelin on the natural course of schizophrenia are full recovery, 4.1%; social remission, 17 %; and deterioration, 70%. There were little variations in these figures during the pre-psychopharmacological era. Thus, Evensen in his first study reported 15% social remissions, a figure somewhat lower than Kraepelin's. His sample consisted of male schizophrenics younger than 26 years first admitted to the Gastaud Hospital between 1887 and 1896. The evaluation was based on a 5-15-year follow-up. After a similar follow-up period on a sample of 815 schizophrenic patients discharged from the Gastaud Hospital between 1915 and

1929, Evensen found that 23% of the patients were self-supportive or in social remission. This was a modest improvement to his own and also to Kraepelin's earlier figures (Evensen 1936). Similar to Kraepelin's are Langfeldt's (1937) figures based on a 7-13-year follow-up study of 100 schizophrenic patients. In his sample, 66% were uncured or worse (just 4% less than in Kraepelin's) and 17% were completely recovered. In his further analysis Langfeld noted that this 14% consisted of patients with an atypical – so-ca1led schizophreniform – clinical picture. Taking off the 14% of patients with schizophreniform psychoses leaves 3% full remission, which is only slightly lower than Kraepelin's figure (Hoenig 1967).

The observation that schizophrenic disorders do not always follow an unfavorable course led Langfeldt (1937, 1939, 1956, 1960, 1969) to the identification of criteria which could distinguish between a bona fide "process schizophrenia" with a bad prognosis and “schizophreniform psychoses" with a good prognosis. The distinction between “process schizophrenia” and “schizophreniform psychosis” has been further substantiated by Stephens, Shaffer and Carpenter (1982) and Vaillant (1964).

Recognition that schizophrenic disorders do not always follow a deteriorating course led to the distinction between schizophrenic and schizophreniform psychoses by Langfeldt (1939, 1956) and to the differentiation of continuous schizophrenia, periodical (recurrent) schizophrenia and shift-like progressive schizophrenia by Snezhnevsky (Nadzharow, 1967; Snezhnevsky and Vartanian, 1971).

Langfeldt's and Snezhnevsky's contributions are based on a three-dimensional model of schizophrenia with consideration to the first three developmental stages of the illness. Most recently, Crow (1980), on pragmatic grounds but with consideration to findings with brain imaging, proposed that distinction should be made within the schizophrenias between a Type I syndrome, characterized by positive symptoms, i.e., abnormal psychological features such as delusions, hallucinations and thought disorder, and a Type II syndrome, characterized by negative symptoms, i.e., diminished or absent normal functions, such as flattening of affect, poverty of speech and loss of volition.

The most important contributions to resolving the heterogeneity of end states of “schizophrenia” were of Kleist (1923, 1960) and Leonhard (1957, 1979). In the course of a four-dimensional analyses of psychopathological symptoms in a large number of schizophrenic patients, both Kleist and Leonhard concluded that schizophrenia consists of two distinct

populations (groups of disorders) referred to as typical and atypical by Kleist and systematic and nonsystematic by Leonhard. The two populations are readily distinguished on the basis of the course of the schizophrenic process. In the nonsystematic schizophrenias, the intermittent periodicity resembles manic depressive illness and in the systematic schizophrenias the "down-hill" course resembles organic dementias. Since Kleist (1960) believed that each subtype is the result of a specific impairment in a different neurological system, he asserted that the schizophrenias are diseases of the brain which may affect several different neurological systems (atypical) or are confined (localized) to one neurological system (typical). Leonhard, on the other hand, emphasized possible genetic differences among the subtypes and the functional rather than the morphological nature of the various disorders.

There was little, if any, interest in Kleist's and Leonhard's classification of schizophrenia prior to the introduction of neuroleptics. It was the recognition that not every schizophrenic benefits equally well from neuroleptics and that long-term neuroleptic administration may induce serious adverse effects such as tardive dyskinesia (TD), skin pigmentation and ocular changes, that lead to an interest in Leonhard's (1957) classification of schizophrenia . It was Frank Fish (1962)) first who classified a chronic schizophrenic population on the basis of Leonhard's criteria and found it useful in the identification of patients therapeutically responsive to neuroleptics. Further interest in Leonhard's system was generated by Astrup (1959, 1962, 1979). He employed a special test battery, consisting of word associations, motor-conditional reflex, defensive finger withdrawal and several other tests, and was able to identify differences in performance among different subtypes of schizophrenia. About the same time Sarro Burbano (1957) in Spain found no difficulties in using Leonhard' system for diagnosing patients.

In an effort to simplify the task of deriving a diagnosis in Leonhard's classification Fish (1964b) devised a guide for the assignment of patients to specific subtypes. Recently, another guide has been developed by Ban (1982).

Nonsystematic vs Systematic Schizophrenias

Within Leonhard's (1979) classification of endogenous psychoses nonsystematic and systematic, schizophrenias represent two distinctly different groups of disorders. Nonsystematic schizophrenias are characterized by rapid onset, multiform clinical manifestations, intermittent

episodic course and relatively favorable outcome with usually mild defect and relatively good working ability. In contrast, systematic schizophrenias are characterized by insidious onset, simple clinical manifestations, processual-progressive course and usually unfavorable outcome with moderate to marked defect and considerably impaired working ability. Another distinguishing feature of the two populations is "double-entry bookkeeping," which if present designates a systematic population (Ban, Guy and Wilson 1984a).

Furthermore, the two schizophrenic populations differ also in respect to cross-sectional psychopathology Prevalent among the varied (diffuse) psychopathological manifestations in patients with nonsystematic schizophrenia are dysthymic and/or hyperthymic mood changes, hallucinations, emotionally loaded delusions and/or multiform catatonic activity. Outcome is characterized by residual symptoms such as blunted affect, circumstantial or vague speech, impaired role functioning, peculiar behavior, social withdrawal and/or unusual social experiences. In contrast, prevalent the systematic schizophrenias are hallucinations with or without hallucinatory excitements, delusions without emotional loading and/or simple catatonic activity, such as ambitendency, automatic obedience, cooperation in movements, mannerisms, mutism, negativism, parakinesis, posturing, proskinesis, rigidity, stereotypy and/or waxy flexibility.

Outcome of systematic schizophrenia is characterized by clinical and/or personality defect.

Systematic Schizophrenias

Within Leonhard's conceptual framework, acute psychotic exacerbations may be seen as dissociation along three psychopathological structures – perceptual-cognitive, emotional- affective and motor-adaptive – with each exacerbation resulting in a gradual “regression” and transition from a higher to a lower level of functioning in one of the structures.

Thus, primarily on the basis of the course of the illness, Leonhard distinguished between a systematic and a nonsystematic schizophrenic population and, with the employment of structure analysis of the clinical features, he divided the systematic population into three categories: catatonias (disorders with prevailingly motor-adaptive psychopathologies), paraphrenias (disorders with prevailingly perceptual-cognitive psychopathologies) and hebephrenias (disorders with prevailingly relational-affective psychopathologies).

Finally, by psychopathological assessment Leonhard identified 16 subtypes within the

systematic population: six catatonic (parakinetic, proskinetic, speech-prompt, speech inactive, manneristic and negativistic), six paraphrenic (phonemic, hypochondriacal, confabulatory, expansive, fantastic and incoherent) and four hebephrenic (autistic, eccentric, shallow and silly) subtypes.

Systematic Catatonias

The six subtypes of systematic catatonia represent different stages in the level of deterioration in motor-adaptive structures and include patients with a relative excess or a relative deficiency in activities. Relative excess of activity may appear as unnatural-awkward voluntary and jerky involuntary expressive movements with facial grimacing in parakinetic catatonia; obedient answering but talking beside the point (*vorbeireden*) with an empty facial expression in speech-prompt catatonia; and autonomic obedience with a monotonous mumbling speech in proskinetic catatonia. In contrast, the relative deficiency of activity appears as impoverished speech, such as mutism or delayed and slow replies in speech inactive catatonia; impoverished involuntary motor activity, such as waxy flexibility or stiff movements and posturing in manneristic catatonia; and an active striving against all attempts at making contact in negativistic catatonia. Thus, among the systematic catatonias negativistic catatonia seems to be the opposite of proskinetic catatonia, manneristic catatonia the opposite of parakinetic catatonia and speech inactive catatonia the opposite of speech-prompt catatonia.

In the differentiation among the subtypes of the catatonic category, most revealing are psychopathological symptoms related to speech. Thus, speech-prompt catatonics respond promptly and without delay. However, they do not show spontaneous loquaciousness and their voluble speech in responding to questions lacks meaningful content. While negativistic catatonics may give partial answers, manneristic catatonics frequently do not talk at all.

There is a jerky pattern of speech with short ungrammatical sentences in parakinetic catatonia; murmuring and verbigeration in proskinetic catatonia; and a continuous whispering to hallucinatory experiences in speech inactive catatonia. Opposition (*gegenhalten*) is seen in manneristic catatonia, cooperation (*mitmachen*) and grasping (*mitgehen*) are exclusive for proskinetic catatonia. Abnormal postures, such as generalized rigidity, waxy flexibility (*haltungsverharen*) and the so-called "psychological pillow," a manifestation of opposition, are

pathognomonic for manneristic catatonia; waxy flexibility may also occur in speech-prompt catatonia. Abnormal spontaneous movements are widespread in this category: grimacing is characteristic of parakinetic catatonia; handling and intertwining of proskinetic catatonia; stereotypes of proskinetic and manneristic catatonia; and impulsive action of manneristic and negativistic catatonia. While speech-prompt and proskinetic catatonics turn toward the examiner in an exaggerated manner (adversion), speech inactive catatonics turn away (aversion), although true negativism is present only in negativistic catatonia.

Differential characteristics among the systematic catatonias are almost exclusively based on the differential motor and speech patterns of the subtypes. Pathognomonic of the negativistic subtype is the association of blunted affect with negativistic excitement and of the manneristic subtype the association of hard mannerisms with well-retained affectivity and lack of hallucinatory and delusional experiences.

Systematic Paraphrenias

The six subtypes of paraphrenia represent different levels of deterioration in perceptual-cognitive structures. The subtypes are on a continuum of severity from phonemic and hypochondriacal through expansive, confabulatory and fantastic to incoherent. With the increase in formal disorder of thinking, there is a corresponding decrease in working ability. Further, there is a shift in affectivity from blunting (phonemic), through depression (hypochondriacal) to meaningless euphoria (expansive, confabulatory and fantastic).

Accordingly, in phonemic paraphrenia, verbal hallucinations commenting on, or talking to the patient are associated with "wooly" thinking, while in incoherent paraphrenia, representing the opposite end of the continuum, massive auditory hallucinations are accompanied by confusion of thinking, incoherence of speech and disordered behavior. In hypochondriacal paraphrenia, the subtype closest to phonemic paraphrenia, verbal hallucinations, fragmented into disconnected phrases, are associated with bizarre bodily hallucinations and a corresponding irritable, morose and dissatisfied mood, while in fantastic paraphrenia, the subtype closest to incoherent paraphrenia, the severe derailment of thinking falls only somewhat short of conceptual disorganization. The patient's mental life is almost totally occupied by fantastic delusions and mixed (auditory, visual, bodily and not infrequently scenic) hallucinations. Compared to the

fantastic paraphrenic who lives in a world without boundaries of life and death (also without time and space), the expansive paraphrenic lives in the physical world of man. Their haughty pose and corresponding grandiose delusions distinguish these patients from the confabulatory paraphrenic, whose vivid and detailed descriptions of alleged experiences appear as fairy tales, especially when experienced as if they happened in dreams.

Fish (1964a) has brought to attention that even in the paraphrenias auditory hallucinations and/or delusions are not obligatory psychopathological symptoms. Expansive and confabulatory paraphrenics do not hear hallucinatory voices; incoherent paraphrenics do not develop delusions. If persecutory delusions develop in phonemic and hypochondriacal paraphrenic patients they are never primary, but secondary to their hallucinatory experiences. The nature and content of hallucinations differ in the various subtypes of the paraphrenic category. Hypochondriacal paraphrenics are seen to speak to voices at times; incoherent paraphrenics speak to voices all the time. Furthermore, fantastic paraphrenics often reveal that they can hear and understand what birds and inanimate objects say. Visual, scenic, and mass hallucinations, as well as delusional misidentifications, are characteristic psychopathological symptoms of patients with fantastic paraphrenia. Sexual bodily hallucinations are characteristic psychopathological symptoms of patients with hypochondriacal paraphrenia. Grandiose delusions are not encountered exclusively in expansive paraphrenia, they may also be present in confabulatory and fantastic paraphrenia. On the other hand, fantastic delusions are only present in fantastic and possibly confabulatory paraphrenia.

Patients belonging to the different paraphrenic subtypes differ in their affect and mood. In phonemic paraphrenia there is slight blunting of emotional responses; in hypochondriacal paraphrenia blunted emotional responses are associated with a somewhat depressed mood; and in expansive, confabulatory and fantastic paraphrenia with euphoria. Probably most important, however, is that in phonemic and hypochondriacal paraphrenics formal thought disorder is usually less severe than in expansive paraphrenics; and while in confabulatory and fantastic paraphrenics there is an interference with thinking, in incoherent paraphrenics goal directed processing of ideas is not present at all.

Differential characteristics among the systematic paraphrenias are based on the nature of hallucinatory and/or delusional experiences. Supplementing these are differences in the quality (formal disorder) of thinking and affective (mood) state.

Systematic Hebephrenias

The six subtypes of paraphrenia represent different levels of deterioration in the perceptual-cognitive structures, whereas the four subtypes of hebephrenia represent different levels of deterioration in emotional-affective structures.

Similar to the paraphrenias, the four hebephrenic subtypes are on a continuum of severity, as reflected in working ability, from autistic and eccentric through shallow to silly. Parallel with this continuum, there is a shift in mood from depressed and irritable (autistic and eccentric) to cheerful and contented (shallow and silly).

Among the four subtypes, autistic hebephrenia is characterized by active avoidance of all contact, off-putting verbal responses and stiff face; eccentric hebephrenia by soft mannerisms, senseless stealing, and hypochondriacal and querulous complaintiveness; shallow hebephrenia by lack of initiative, and apathetic indifference and silly hebephrenia by inane giggling, spiteful tricks and restless behavior. In spite of the extreme flatness of affect and lack of initiative, there are episodic hallucinatory excitements in patients with shallow hebephrenia. As senseless hoarding is indicative of eccentric hebephrenia, hallucinatory excitement is indicative of shallow hebephrenia.

Differentiation among the systematic hebephrenias is based on the primary characteristics of the illness, such as immature behavior (silly), emotional impoverishment (shallow), soft mannerisms (eccentric) and empty autism (autistic). Two of these subtypes, silly and autistic, display episodic irritability and/or aggression and two, shallow and eccentric display episodic hallucinatory behavior.

Nonsystematic Schizophrenias

In Leonhard's (1957, 1979) classification nonsystematic schizophrenias are one of the five major groups of disorders within the endogenous psychoses and "systematic" and "nonsystematic" schizophrenias are two different groups of diseases. In contrast to the systematic schizophrenias which show no polarity, non- systematic schizophrenias share common features with the cycloid psychoses, a group of bipolar disorders perceived by Leonhard as being on the continuum between the phasic-affective type of psychoses and the schizophrenic type of psychoses.

Nonsystematic schizophrenias consist of three distinct disorders: cataphasia, affect-laden paraphrenia and periodic catatonia. In cataphasia, also referred to as schizophasia, there is a striking dissociation between the disordered or confused speech and thought, and well-preserved behavior with an appropriate affective response (Kleist and Schwab 1950). The clinical picture is analogous to schizophasia described independently by Kraepelin (1913) and Kleist (1930, 1939). Kraepelin pointed out a severe confusion of linguistic expressions despite well-ordered behavior, while Kleist emphasized the presence of neologisms and word confusion, which rarely appear in Kraepelin's description. Thus, in patients with cataphasia behavior is characteristically more coherent than speech and responses to questions more understandable than spontaneous speech production. While some patients with cataphasia may display agitation, pressure of speech, confusion, asyntaxis, paralogia, paragrammatism and/or neologisms, other patients may be taciturn and mute and exhibit a dull and empty facial expression. Depending on the prevailing manifestations cataphasia is subtyped into an excited and an inhibited form.

In affect-laden paraphrenia, which corresponds with Kraepelin's (1919) paraphrenia systematica and Kleist's progressive reference psychosis, pathology of affectivity plays a central role. Delusions or disorder of thought content are secondary to the pathologically-changed affect. Verbalization of the delusional material may lead to irritability, enthusiasm or, in some cases, to threatening verbal, attitudinal or physical behavior. Thus, in contradistinction to cataphasia, in affect-laden paraphrenia there are primary affective changes (anxiety, irritability, ecstasy) and secondary delusions (reference, grandeur, fantastic, mixed) with a paralogical (or logical) systematized (or non-systematized) delusional structure. Pathognomonic of affect-laden paraphrenia is the fluctuating affective state with emotionally charged delusions, i.e., strong delusional dynamics. Prevailing manifestations are anxiety, irritability, delusions of reference and fantastic delusions; or ecstatic mood and grandiose delusions; or a fluctuating affective state with mixed delusions. Depending on the prevailing clinical features, affect-laden paraphrenia is subtyped into an anxious, an ecstatic and a bipolar form.

In periodic catatonia, the third disorder of nonsystematic schizophrenias, motor behavior is primarily disturbed. There is an unusual mixture of excitatory and inhibitory symptoms, associated with episodic hyperkinesia or hypokinesia. In extreme cases there is akinetic stupor. Characteristically there is a decrease or increase of expressive and/or reactive movements with a loss of harmony of natural movements. Other manifestations include parakinesis, motor and

postural stereotypy, impulsive acts, negativism, hyperkinesia, hypokinesia, akinesia and/or mixed kinesia. Depending on the prevailing clinical features periodic catatonia is subtyped into an excited, an inhibited and a mixed form.

There is a strong similarity between the three disorders of nonsystematic schizophrenia and cycloid psychoses: cataphasia resembling confusion psychosis, affect-laden paraphrenia resembling anxiety-elation psychosis and periodic catatonia resembling motility psychosis. The signal difference between the two groups of disorders is related to outcome with full recovery in cycloid psychoses and residual symptoms in the nonsystematic schizophrenias (Ban, Guy and Wilson l984a).

In ICD-9 all schizophrenic disorders are grouped under schizophrenic psychoses without distinguishing between the groups of nonsystematic and systematic schizophrenias. Within this all-embracing group of disorders there are 10 different types of schizophrenic illnesses described. Of these 10 types, there is some correspondence between the simple and hebephrenic types of schizophrenia in the ICD-9 and the hebephrenic category of Leonhard; the catatonic type of ICD-9 and the catatonic category including periodic catatonia of Leonhard; the paranoid type of ICD-9 and the paraphrenic category of Leonhard; and the schizoaffective type of ICD-9 and affect-laden paraphrenia of Leonhard. While Leonhard's classification has no corresponding diagnoses for latent schizophrenia, residual schizophrenia, other schizophrenia and unspecified schizophrenia, ICD-9 has no corresponding diagnoses for cataphasia or for any one of the 16 subtypes of systematic schizophrenia (which are adapted in the DCR).

Similar to ICD-9, in DSM-III, too, all schizophrenic psychoses are grouped under schizophrenic disorders without distinguishing between the groups of nonsystematic and systematic schizophrenias. In contradistinction to ICD-9, however, within this all-embracing group of disorders there are only five different types of schizophrenic illnesses. Of these five types, there is some correspondence between the disorganized type of DSM-III and hebephrenic category of Leonhard; catatonic type of DSM-III and catatonic category, including periodic catatonia of Leonhard; and paranoid type of DSM-III and paraphrenic category including affect-laden paraphrenia of Leonhard. While Leonhard's classification has no corresponding diagnoses for the undifferentiated and residual type, DSM-III has no corresponding diagnoses for cataphasia or for any one of the 16 subtypes of systematic schizophrenia.

Treatment of Schizophrenic Disorders

Pharmacotherapy vs Other Treatments

Progress in clinical psychopharmacology has focused attention on the heterogeneity of the schizophrenic population. It has also revealed that schizophrenia consists of at least two major groups of disorders. Research in clinical therapeutics, however, has not gone beyond the unitary concept of schizophrenia.

Pharmacotherapy offers higher reliability, easier accessibility, greater simplicity and fewer hazards than any other treatments known today. Pharmacotherapy is certainly the treatment of choice for acute and chronic schizophrenics in the community where uncontrolled pathological behavior is unacceptable. It is also the most effective means of shortening the patient's stay in the hospital and of preventing future readmissions (Lehmann 1975).

By now the superiority of pharmacotherapy over physical treatments – insulin-induced hypoglycemia and ECT – has been shown convincingly (Heinrich, Kretschmar and Kretschmar 1972). However, ECT may still be tried if schizophrenic patients fail to improve after three months or more on pharmacotherapy. Similarly, there is substantial evidence to believe that pharmacotherapy is superior to individual psychotherapy, group psychotherapy and milieu therapy (May 1968). Nevertheless, a combination of these therapies with pharmacological treatment may be more effective than pharmacotherapy alone, especially during the rehabilitation and maintenance phases of treatment (Hogarty and Goldberg 1973). The same applies to behavior therapy which has been found useful primarily in the treatment of chronic institutionalized schizophrenics (Liberman 1971).

The pharmacological agents most specifically effective in schizophrenia are the neuroleptic drugs, also referred to as antipsychotics or major tranquilizers.

Pharmacotherapy with Antipsychotic-Neuroleptics

With the rapidly growing number of neuroleptics it would be important that every new neuroleptic has a better therapeutic index and/or a different therapeutic profile than chlorpromazine, or any of the other clinically used neuroleptic drugs. These therapeutic expectations have not been fulfilled. To date all attempts to establish differential clinical effects

among neuroleptics have fallen short. In spite of this, clinical observation indicates that a particular patient, unaffected by a specific neuroleptic, may respond to another neuroleptic drug.

There are no predictors of therapeutic responsiveness to neuroleptics and there is no evidence for a relationship between biochemical changes and therapeutic effects. There are indications, however, that there is a relationship between the changes in the principal urinary metabolites of indoleamines and catecholamines and the side effects induced by neuroleptics. Decrease in VMA is frequently associated with hypotensive manifestations, increase in 5HIAA with gastroenteral side effects and increase in HVA with akinetic or akinetic-hypertonic symptoms (Ban 1973).

It is disappointing that there are no reliable clinical predictors of therapeutic responsiveness to neuroleptics. In one study, thioridazine was found to be therapeutically more consistently effective in patients with a poor premorbid adjustment (Judd, Goldstein, Rodnick and Jalkson 1970), while in another chlorpromazine was found to be more consistently effective in patients with a good premorbid adjustment (Klein and Rosen 1973). Similarly, in the study of Goldberg, Klerman and Cole (1965) the "withdrawal dimension" could be affected by neuroleptic drugs only, while in another study the "negative (withdrawal) symptoms," such as blunted affect, poverty of speech and social withdrawal were found to respond to social therapies (Wing, Leff and Hirsch 1973). As the "florid symptoms" of schizophrenia are associated with Schneider's (1957) "first rank symptoms" (thought insertion, thought broadcasting, thought withdrawal, delusional perceptions, delusions of control, auditory hallucinations), the possibility has been raised that it is the "first rank symptoms" which can be controlled by neuroleptic drugs only. Nevertheless, Abrams and Taylor (1973) found no relationship between the presence of "first rank symptoms" and therapeutic responsiveness to neuroleptics.

In spite of the fact that the percentage of "symptom free" schizophrenic patients has not been increased by the introduction of neuroleptic drugs and the therapeutic changes have been confined to a shift from the prevalence of "psychotic" to the prevalence of "residual symptoms" (Kelly and Sargant 1965), there is an impressive consensus that the treatment of choice for schizophrenia is pharmacotherapy with neuroleptics (Cawley 1967). The lack of increase in "symptom free" schizophrenic patients corresponds with the findings that the rate of remission has remained essentially unchanged during the past 55 years (Kraepelin 1899; Simon, Wirt, Wirt and Halloran 1965), although the discharge rate from hospitals has

considerably increased. The increased discharge rate from hospitals, regardless of the presence of psychopathological symptoms, may explain the higher social remission rates found by Gross, Huber and Schuttler (1971) (eight- and four-year follow-up) studies carried out after the introduction of new drugs. Nevertheless, the fact remains that social recovery in Achte's (1961) four-year follow-up study on patients admitted between 1953-1955, i.e., prior to the introduction of neuroleptics, is higher (65%) than in these two later reports.

Neuroleptics and Etiological Speculations

One of the most important contributions to schizophrenia research which has resulted from psychopharmacologic progress is the verification that schizophrenia consists of a biologically heterogenous population. In view of this it is paradoxical that the most extensively explored biochemical hypothesis, the DA excess hypothesis, deals with "schizophrenia" instead of one or another subtype of the schizophrenias.

Dopamine Excess or Deficiency

The finding that "clinical potencies" (mg/kg therapeutic dose requirements of neuroleptics) correlate well with binding affinities at DA_2 receptors prompted several laboratories to search for alterations in the levels of DA and/or DA receptors in post-mortem brains of schizophrenic patients. As a result, a significantly increased number of DA_2 receptors (Owen, Cross, Crow et al. 1978), as well as a 50% increase in DA content, was found in schizophrenic brains (Bird, Barnes, Iversen et al. 1977). There are indications, however, that the increase in the number of DA_2 receptors may be related to prior treatment with neuroleptic drugs.

In favor of the hypothesis that DA excess is related to the psychopathology in schizophrenic patients are the findings that schizophrenic psychopathology may be precipitated and/or aggravated by the administration of DA releasers, such as methylphenidate or ethanol. In favor also is that the therapeutic effects of neuroleptics may be potentiated by adding substances which interfere with the formation and/or action of DA to the treatment regime such as alpha-methyl-p-tyrosine (AMPT) (a specific tyrosine hydroxylase inhibitor) or alpha-methyldopa (a non-specific dopa decarboxylase inhibitor) (Snyder 1976). On the other hand, and in variance with the

DA excess hypothesis, are the findings that the time of onset of amphetamine psychosis (which serves as the model psychosis for schizophrenia) coincides more closely with DA depletion than with increased DA availability. In variance also are the findings that in some schizophrenic patients, amphetamine administration alleviates psychotic symptomatology and in others it enhances the therapeutic effect of neuroleptics (Fukuda and Mitsuda 1979; Van Kammen, Docherty, Marder et al. 1982).

Prostaglandin: Deficiency or Excess

In keeping with the DA excess hypothesis, is the prostaglandin (PG) deficiency hypothesis of schizophrenia. The link between the two is prolactin, a potent stimulator of PG synthesis. Since the release of prolactin is controlled by DA, the neuroleptic-induced DA receptor blockade produces prolactin excess and increase in PG synthesis.

The hypothesis that schizophrenia is a PG deficiency disease is based on observations that schizophrenic patients are relatively resistant to pain and inflammation and are free of rheumatoid arthritis, a disorder in which PG plays an important role. In favor of the hypothesis are findings that PG antagonists (chloroquine, quinine, quinacrine) may, in high doses, induce schizophrenic-like states and that therapeutically effective neuroleptics stimulate the production of prolactin, while drugs which precipitate or aggravate schizophrenia (levodopa, cortisol) suppress secretion and/or block prolactin effects (Horrobin 1977). Further, in two pilot studies, penicillin, which mobilizes dihomo-gamma-linolenic acid (DGLA), the rate limiting step in PGE1 synthesis, has shown some therapeutic effects in chronic schizophrenic patients (Chouinard, Annable and Horrobin 1978).

Conversely, it has been suggested that schizophrenia is a disease of PG excess, i.e., the result of an excessive release of PGE1 into the hypothalamus with an accompanying elevation of temperature (Feldberg 1976). Although there was no indication whatsoever that that paracetamol – a substance which reduces PGE1 levels – has any therapeutic effect in acute schizophrenic patients, Gjessing (1953) reported febrile episodes in two-thirds of his special group of catatonic patients.

Endorphins: Excess or Deficiency

The endorphin excess hypothesis of schizophrenia is in keeping with the PG deficiency hypothesis. Terenius, Wahlstrom, Lindstrom and Widerlow (1976) found elevated alpha endorphin levels in the CSF of schizophrenic patients. Furthermore, endorphins were shown to block the mobilization of DGLA and the formation of PGE1 resulting in a diametrically opposite effect to that of prolactin on PG synthesis. As successful neuroleptic treatment decreased CSF endorphin concentrations, a positive relationship was suggested between CSF endorphin concentrations and schizophrenic psychopathology. Further, as naloxone, by occupying endorphin receptors, has reversed endorphin induced catatonia (in animals), the possibility has been raised that naloxone may have a place in the treatment of schizophrenia. However, the initial favorable therapeutic effects of intravenous naloxone administration on schizophrenia could be replicated only in two out of eight clinical experiments.

Conversely, it has been also suggested that decreased availability of endorphin to the cerebral opiate receptor sites is responsible for schizophrenic psychopathology (Jacquet and Marks 1976). Within this frame of reference, schizophrenic psychopathological symptoms are perceived as the result of a deficiency in the production of an endogenous neuroleptic peptide which can be replaced by exogenous neuroleptic drugs. In favor of this hypothesis is the opiate receptor binding property of endorphins and neuroleptics and the finding that of all CNS regions, the striatum has the highest opiate-binding capacity. In favor also were the findings that, in at least three schizophrenic patients, intravenous endorphin administration produced a reduction (and/or disappearance) of auditory hallucinations, paranoid ideation and pathological pressure of thought (Kline, Li, Lehmann et al. 1977).

The controversy regarding the role of endorphins in schizophrenic psychopathology is far from being resolved (Pethö, Graf, Karciag et al. 1982; Volavka, Mallya, Gaig and Perez-Cruet 1977).

Neuroleptics: Long-term Effects

Regardless of these hypotheses, or rather speculations, the fact remains that neuroleptics have considerably transformed the prevailing manifestations of schizophrenic disease. While this

transformation did not change the distribution of subtypes in in Leonhard's classification (Ban, Guy and Wilson 1984a), the discharge patients from the hospital into the common population led to an increase in fertile marriages among community-based schizophrenics (Erlenmeyer-Kimling, Nicol, Rainer and Demic 1969). This is not expected to lead to an abrupt rise in the incidence of schizophrenia but might lead to an eventual increase in the proportion of persons who may be affected.

Irrespective of its possible social consequences, long-term treatment with neuroleptics may produce serious adverse effects. While skin pigmentation occurs in less than 0.1% of all patients treated with phenothiazines for a period of two years or more (Lehmann and Ban 1974), the estimated incidence of ocular changes is as high as 20-35% in patients receiving phenothiazines over an extended period. The prevalence of TD, the most serious long-term complication, ranges from 0.5-40% (Ban 1979).

One possible way to reduce the occurrence of these complications is a more discriminate use of neuroleptic drugs. While there is little, if any, evidence that patients with different types of schizophrenia, as classified by DSM-III or ICD-9, would respond differentially to neuroleptics, there are indications for differential therapeutic responsiveness to neuroleptics in Leonhard's different subtypes.

Neuroleptics and Leonhard's Classification

The possible relationship between therapeutic responsiveness and Leonhard's subtypes within the schizophrenias was first recognized by Astrup (1959) and demonstrated by Fish (1964a). In a survey including 474 chronic schizophrenic patients Fish found that in both the nonsystematic and systematic schizophrenic populations catatonic patients responded to neuroleptics less favorably than the others and within the systematic schizophrenic population hebephrenic patients responded less favorably than paraphrenics.

There seems to be also a relationship between therapeutic dose requirements and Leonhard's subtypes (Ban, Guy and Wilson 1984b). In a survey of 768 patients, carried out in eight countries it was found that mean daily dosages in the nonsystematic and systematic populations were similar while within the nonsystematic population mean daily dosages of patients with cataphasia were more than twice as high than in affect-laden paraphrenia and almost four times as

high than in periodic catatonia. While there was little difference in mean daily dosages among the three systematic schizophrenic categories, there was a wide variation in mean daily dosages among the subtypes within each category. In the four paraphrenic subtypes, mean daily dosages were highest in phonemic and incoherent paraphrenia and lowest in the expansive and confabulatory subtypes. In the four hebephrenic subtypes, mean daily dosages were highest in the eccentric and lowest in the speech inactive and parakinetic subtypes.).

In keeping with the differential therapeutic responsiveness in different subtypes are the observations in a patient with the diagnosis of periodic catatonia (febrile catatonia) in whom an increase in neuroleptic dosage was associated with exacerbation, a decrease in dosage with amelioration and discontinuation of medication with remission of psychopathological symptoms (Kelwala and Ban 1981a).

In another case report on two patients with diagnoses of shallow hebephrenia, a systematic subtype, discontinuation of neuroleptic medication for an extended period (Kelwala and Ban 1981b) had no detectable effect.

The notion that neuroleptic treatment in certain patients may not merely be ineffective but may actually be harmful received substantiation in a survey of 24 patients treated with lithium/neuroleptic combinations. Analyses of data revealed that 9 of 10 patients of the non-systematic schizophrenic population exhibited a favorable therapeutic response to the addition of lithium whereas 9 of 14 of the systematic schizophrenic population showed no response or an unfavorable therapeutic response. Furthermore of the 14 patients with systematic schizophrenia 9 developed neurotoxicity (confusion)) to the addition of lithium to their neuroleptic treatment whereas in the non-systematic population in none of the patients was neurotoxicity seen (Prakash, Kelwala and Ban 1982).

Probably the most important finding in this study, however, is a possible inverse relationship between therapeutic and chronic adverse effects (Guy, Ban and Wilson 1985). No patient with the diagnosis of expansive and confabulatory paraphrenia, neuroleptic-responsive populations, developed TD in the course of treatment whereas the highest incidence of TD was encountered in parakinetic catatonia, a subtype unresponsive to neuroleptics receiving relatively low mean daily dosages of neuroleptics. Furthermore, the incidence of TD was significantly ($p<.001$) lower in the nonsystematic than in the systematic patient group.

In spite of effective neuroleptic treatments the distribution of Leonhard subtypes in 768

chronic hospitalized patients contributed by nine centers, located in eight countries, representing four continents, remained similar in the early 1980s (Ban, Guy and Wilson 1984a) to the distribution of the subtypes in hospitalized populations of similar size in the late 1930s (Leonhard 1957) and in the early 1960s (Astrup 1979; Ban, Guy and Wilson 1984a).

It is a common contention that psychopharmacology opened unforeseen possibilities for progress in schizophrenia research. A re-evaluation of current concepts of "schizophrenia" with special emphasis on the different disease forms represented by the different “end-states” could open unforeseen possibilities for psychopharmacologic progress with a shift of emphasis from studying therapeutic efficacy, based on statistical probabilities, to the identification of therapeutically-responsive schizophrenic patients to specific treatment modalities.

In 1960, Flach, Liang and Stokes noted the significant decrease in urinary calcium excretion in those paranoid schizophrenic and depressed patients who showed a favorable therapeutic response to the tricyclic antidepressant, imipramine, or electroshock (Flach 1964). It remains to be seen whether this antidepressant responsive schizophrenic population represents a distinct subtype within the schizophrenias.

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