

# Schizophrenia: A Concept

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## Abstract

Much of the current research-work into biological basis of mental disorders is predicted on implicit concept of disease that is less critical and sophisticated as it should be. It is remarkable, how the fundamental conceptual frame work of schizophrenia, as proposed by Professor Emil Kraepelin has stayed the same, since its inception almost 100-years ago. This review explores these issues besides highlighting alternative disease classification that suits behavioural neuroscience research.

## Introduction

Schizophrenia is one of the few syndromes that have managed to keep itself veiled in scientific mystery, even after 100-years of research and inquiry. Labeled as grave yard of psychiatry; it has generated much controversy with plethora of theories and hypothesis attempting to answer many questions. It is remarkable that many of the current research ideas are in fact, rediscoveries, of early observations and hypotheses, many of them datable to the first decade following the Professor Emil Kraepelin's diagnostic scheme in 1896.<sup>1</sup>

This review aims to explore the different themes pertinent to nosology, epidemiology and research of Schizophrenia. It intentionally aims to violate the traditional boundaries of neurology and Psychiatry in order to embrace an interdisciplinary perspective. Firstly, we will examine the historical perspective regarding the concept and epidemiology followed by discussion on current and alternative conceptualization of schizophrenia.

## Historical aspect of Schizophrenia concept

Madness is mentioned in ancient texts such as the Hindu Ayur Veda and the Old and New Testament. In the writings dating from the second century AD of Aretaeus the Cappadocian it is discussed at length. However, although the descriptions of melancholia and its switch into hilarity are easy to recognize, as what would now be called Bipolar affective disorder. First unambiguous description of symptoms suggestive of schizophrenia was given by Haslam and by Pinel in 1809. Throughout the nineteenth century many attempts were made to classify insanity. In 1856 Morel introduced the term dementia praecox to

describe an adolescent patient once bright and active, who had slowly lapsed into a state of withdrawal.<sup>1</sup>

Many other psychiatrists wrote descriptive accounts of the clinical pictures presented by their psychotic patients but in 1890 Emil Kraepelin<sup>2</sup>, Professor of Psychiatry in Heidelberg and Munich, went beyond straightforward clinical description and divided the broad class of functional psychoses into two categories, essentially on the basis of outcome. The first category, which he called manic-depressive insanity, pursued a fluctuating course with frequent relapses but with full recovery between episodes. The second, for whom he used Morel's term dementia praecox, embraced catatonia as described by Kahlbaum (1874), hebephrenia which had been described by Hecker (1871) and his own dementia paranoides.<sup>2</sup> Kraepelin grouped these together as different manifestations of a progressive disease which either pursued a steady downhill course to a state of chronic impairment, or if improvement did occur resulted only in partial recovery. In grouping together the mental illnesses of early adult life associated with poor outcome, Kraepelin considered that he was defining a clinical syndrome which represented a disease of the brain the nature of which would be revealed by appropriate investigations.

In 1911 Eugen Bleuler published his Dementia praecox or the group of schizophrenias and it is his term of schizophrenia that has received general acceptance. Although Bleuler considered that he was developing Kraepelin's concept in fact he changed it substantially.<sup>3</sup> Bleuler was influenced by psychoanalytic schools of thought and described the concept of schizophrenia in psychological terms as much as in the neuropathological one, as envisaged by Kraepelin. His term schizophrenia, meaning split mind, was intended to describe what he called a loosening of the associations between the different functions of the mind so that thoughts became disconnected and the coordination between emotional, cognitive and volitional processes became poor. He considered thought disorder, affective disturbance, autism, and ambivalence to be the fundamental symptoms of schizophrenia and that the more clear-cut phenomena of hallucinations, delusions, and catatonic features emphasized by Kraepelin were of lesser importance. This view led him to conclude that schizophrenia could be diagnosed when there was no

**Table 1. Three features of schizophrenia.**

1. The presence of specific types of delusions or hallucinations or thought disorder, e.g. Schneider's first rank symptoms.
2. The absence of primary mood change.
3. Chronic deterioration of function.

**Table 2. Schneider's 'symptoms of the first rank'<sup>4</sup>**

1. Hearing one's thoughts spoken aloud in one's head.
2. Hearing voices arguing.
3. Hearing voices that comment on what one is doing.
4. Experiences of bodily influence (that bodily functions are affected by an outside agency).
5. Experiences that one's thoughts are withdrawn or that thoughts are inserted into one's mind.
6. Thought diffusion or the experience that one's thoughts are broadcast to other.
7. Delusional perception (the attribution of special significance to a particular perception).
8. Feelings or volitions experienced as imposed on the patient by others.

evidence that hallucinations or delusions had ever occurred and he thus added simple schizophrenia to the hebephrenic, catatonic, and paranoid forms recognized by Kraepelin.<sup>3</sup>

These findings and others have encouraged the formulation of operational rules for defining schizophrenia. Such systems specify whether or not an individual patient will be placed within that particular definition of schizophrenia according to the presence or absence of a given set of features. In spite of Bleuler's views, in the last 20 years, the diagnosis of schizophrenia has generally been considered only in the presence of psychotic features, i.e. delusions, misperceptions, and/or thought disorder.

Once these features are present, three separate areas of dysfunction may be used in making the decision that a patient has schizophrenia (Table 1). Symptoms of the first rank (also known as unclear symptoms) were defined by Kurt Schneider (Table 2).<sup>4</sup>

According to Schneider these symptoms by themselves could identify an illness as unequivocally schizophrenic. However the force of this assertion was somewhat diminished by the recognition that they can occur in some other conditions such as amphetamine psychosis and the psychoses of temporal lobe epilepsy. Although Schneider denied that these symptoms necessarily had a particular significance in relation to the nature of the disease process and indeed regarded them merely as a pragmatic basis for diagnosis, several symptoms relate to the peculiarly schizophrenic experience in which the contents of consciousness can arise from or be directly influenced by agencies other than the self.

## **Epidemiology: Past and present**

It is of interest to note how early epidemiological studies of schizophrenia were actually conducted 'in the field'. The majority were carried out single-handedly by dedicated researchers who typically spent months and sometimes years in a community, collecting information and interviewing, literally, door-to-door. For example, Graemiger (1931), a Swiss general practitioner working in rural community, published 66 extended genealogies segregating psychotic illnesses and claimed to have known personally 1357 of their members across four generations. Personal knowledge of respondents, access to multigenerational records from the local Parish registers, and generous cooperation by the community as a whole resulted in detailed and accurate data of a descriptive quality that would be difficult to match today.<sup>5</sup>

Probably, the first application of the epidemiological method in a modern sense, to the investigate psychosis was the work of female physician, Jenny Koler, who in 1895 conducted a case-control study on the aggregation of psychiatric disorders in the families of 284 probands and 370 healthy control subjects in Zurich (Koller, 1895). In many ways, her conclusion anticipated present day knowledge about genetic epidemiology of psychosis. She found that 'the hereditary loading of healthy subjects is much higher than generally assumed'; that 'the strongest loading is that of psychosis and accentuated characters'; and that 'the loading in distant relatives is quite low, unless a person at risk is exposed to multiple factors'.<sup>6</sup>

Many of the results of those early studies retain their benchmark value today. As a matter of fact, none of the more recent contributions from the epidemiological research has substantially altered the conclusions of the earlier studies. These include the population incidence and prevalence of schizophrenia, the age at onset curve, the age- and sex-specific morbid risk, the morbidity risk for specified biological relatives of schizophrenia probands, the outcome of dual matting of individuals with psychoses, and the data on reduced fertility of person with schizophrenia.<sup>6</sup>

Estimate of incidence and prevalence of Schizophrenia depends on the criteria for diagnosis and the population surveyed. Disorder of schizophrenia emanates from a concept - which might be narrow or broad. Literature is replete with examples - how the diagnostic conventions were different in United States and United Kingdom. Cross country studies, using operational diagnostic criteria have been able to answer some of the questions.

A World Health Organization's study of ten countries found a rather consistent annual inception rate for schizophrenia ranging from 0.07 per 1000 in Aarhus, Denmark, to 0.14 per 1000 in Nottingham, United Kingdom

(Jablensky et al. 1992).<sup>7</sup> The annual incidence is probably between 0.1 and 0.5 per 1000 population. The lifetime risk of developing schizophrenia is probably between 7.0 and 9.0 per 1000. The point prevalence of schizophrenia in European countries is probably between 2.5 and 5.3 per 1000 (Jablensky). Collaborative studies of World Health Organization have shown that prevalence of schizophrenia, when assessed in comparable ways, is similar in different countries.

## Concept of Schizophrenia

It is important to understand that current concept of schizophrenia is based on phenomenological symptoms elicited by detailed psychiatric interview. This is based on Kraepelin's delineation of Dementia praecox and Manic-depressive illness from functional psychosis. Historically, the psychosis has been divided into two broad groups: organic (e.g. Alzheimer's disease, epileptic psychosis), and functional psychosis. The historical basis of this division was simple, and rested on the presence of readily identifiable brain pathology or a well-documented electrophysiological or metabolic disturbance in the organic psychosis. Advances in imaging techniques have improved physicians' ability to detect subtle pathology where none was previously suspected; therefore, the concept and practice of assigning syndrome like schizophrenia to the category of functional psychosis is obsolete.

Almost half a century ago Longo (1952) wrote that "it is uncontroversial that in the brain of schizophrenics have been found different kind of histopathologic alterations; however these alterations cannot be considered

rigorously specific of the disease but they are unequivocal evidence of an ongoing organic process. Therefore, schizophrenia is not to be considered any more a psychodegenerative or psychogenic illness but a true organic disease of the nervous system".<sup>8</sup>

This is another sense in which history of schizophrenia is at odds with rest of the medicine: the fundamental conceptual framework within which schizophrenia research has been conducted. i.e. the Kraepelinian dichotomy of major psychoses, has hardly been modified since its inception. Its essential features are present in ICD-10 (WHO, 1993) and DSM-IV (APA, 1994). Prominent researchers and teachers indicate an allegiance to this "neo-Kraepelinians' school of thought. However, it is generally accepted that there is no single test or procedural rule to establish the validity of disease concept or of a diagnostic classification in psychiatry (Kendell, 1975).<sup>9</sup> The acceptance of a particular diagnostic concept or a classification scheme is usually based on the interpretation of converging evidence from multiple sources, including descriptive psychopathology, neuropathology, pathophysiology, genetics and epidemiology. This process bears a similarity to the way that 'paradigms' evolve in science (Kuhn, 1962).<sup>10</sup>

After discussing the recurrent themes and conceptual issues in the nosology of schizophrenia, let us now go beyond conventional boundaries of disciplines in medicine, in order to explore the issues pertinent to research.

## Cognitive abnormalities in schizophrenia

Cognitive function in schizophrenia is characterized by a background of generalized impairment (I.Q is generally a standard deviation lower than expected), with poor performance on attention, memory, abstract thinking, spatial working memory, and executive functions. These deficits are present at the onset of illness, persist despite clinical improvement, and are not the result of emotional or motivational problems. Supporting evidence is the fact that frontal lobe injuries (particularly dorsolateral prefrontal cortex [DLPFC]) in adult life can mimic the 'deficit syndrome' of schizophrenia.<sup>11</sup>

In one landmark study, Crow and Done, followed up on all of the more than 15,000 children born in UK in one week in March 1958. Subjects were tracked from their mother's pregnancies until the present time by health visitors. Socially, individual (especially boys) who experienced schizophrenia as adults were already rated by teachers at age 7-years as manifesting more maladjustments than peers; preschizophrenic girls were rated as more withdrawn and depressed at age eleven. I.Q was 5 to 10 points lower than expected, and the children were reading



Figure 1: Perceptual disorder, as envisioned by a patient with Schizophrenia: Painted by Dr. Ali Wasif, consultant psychiatrist.

impaired at age 7 years. Neurologically, these children showed delayed development of handedness preference even at the age of 11 years.<sup>12</sup>

### **Neurological Abnormalities**

Although neurological examination may reveal minor asymmetries of reflexes in schizophrenic patients, the conventional examination of patients with this disorder yields rather little if one depends on data obtained with reflex hammer, ophthalmoscope, and tuning fork, the classic armamentaria of the neurologist. Unobtrusive observation yield much more.

The most consistent neurological sign beyond the abnormalities of the mental state found in both early and late schizophrenia are in the domain of ocular movement. Since pseudo-Parkinsonism, induced by Neuroleptic agent, and tardive dyskinesias following prolonged use or withdrawal of such agents may be associated with eye signs, neurological evaluation should precede initiation of drug treatment

### **Ocular signs**

Absence and avoidance of eye contact and staring for long periods into space are the most common ocular signs observed in schizophrenic patients. Similar staring is commonly observed as the very first indication of a seizure arising in the amygdala in man, but may also be the only sign of petit mal epilepsy. In the latter, in contrast to amygdala seizures and schizophrenia, a characteristic cortical EEG discharge is always present.

Most normal adults blink six to 12 times per minute. Nearly one-half of the patients with acute untreated schizophrenia have decreased, increased, or paroxysmal bouts of rapid blinking. In patients with chronic schizophrenia, steady blinking at 60 to 80 times a minute is not uncommon. This is in contrast to psychomotor epilepsy, during which similar episodes of blinking may occur. Such events can be readily interrupted in schizophrenic patients.<sup>13</sup>

It is of interest to note that blink reflex to even the first glabellar tap is often absent in acute untreated schizophrenics. In contrast, patients with central DA depletion, or patients receiving Neuroleptic DA-blocking agents, usually fail to habituate the glabellar reflex and display untiring blinks to repeated glabellar taps. Since persistence of the blink reflex (but decreased on absent spontaneous blinking) is usually an early index of DA depletion or blockade, absence of the glabellar reflex prior to treatment may be sign of DA hypersensitivity or hyperactivity in systems inhibiting the blink reflex.<sup>14</sup>

### **Neurological Soft Signs**

Neurological soft signs refer to subtle neurological abnormalities comprising deficits in sensory integration, motor coordination, and sequencing of complex motor acts. A considerable body of research has established that neurological soft signs are prevalent in schizophrenic patients, including first-episode cases, than in health subjects. Studies with Neuroleptic-naïve first episode patients have demonstrated that neurological soft signs are present before medication exposure, thus they are thought to be an intrinsic feature of schizophrenia. This notion is supported by findings of neurological soft signs in high-risk subjects (i.e., relatives of schizophrenic patients and unaffected co-twins of monozygotic twin pairs discordant for schizophrenia). Studies generally found that relatives take an intermediate position between healthy and schizophrenic subjects.<sup>15-17</sup>

### **Structural Brain changes**

Modern neuroimaging techniques have shown that virtually every brain region is affected in schizophrenia. Both chronic and first-episode, undedicated patients show widespread, if small, alterations in ventricular size and cortical grey matter. Compared with approximately 5% overall grey matter alterations, schizophrenic patients manifest more disproportionate local brain changes, generally in the range of 15%, in the mesial temporal, temporal neocortical, prefrontal, and parietal regions, with possible alterations in thalamus, basal ganglia and cerebellum.<sup>18-20</sup> Many of the prominent volume changes and asymmetry disturbances in schizophrenia may lie within the heteromodal association neocortex, a neocortical system that includes the planum temprale, DLPFC, Broca's area, and inferior parietal lobule.<sup>21-24</sup>

### **Beyond boundaries: Research issues**

Traditionally, schizophrenia is divided in to five subtypes based on the phenomenological symptoms. This categorization does have its utility in being able to predict treatment and prognosis. However, the major stumbling block for researchers may be the definition of disease phenotype. Though the classical clinical picture of schizophrenia based on delusions and hallucinations can be vivid, one contributing factor to the failure to identify a susceptible gene may be that classical symptoms-based disease phenotype is too narrowly defined and too heterogeneous and classical disease phenotype are not stable over time. This problem led many researchers to propose employment of heritable physiological or neurobiological traits, correlated with the disease as the phenotype. Such intermediate or endo-phenotypes, some times referred as biomarkers, are proposed to have

simplistic utility, improved operational definitions, and for some, more objective diagnosis.<sup>25</sup>

Although this proposition is still in its infancy, an emerging consensus among investigators is that the most useful candidate biological marker for schizophrenia are those that are more frequent in patients than control population; that are stable over time and insensitive to age, gender, and medication status; that are more frequent in non-schizophrenic members of multiple affected families than control populations. Possible candidates for biological markers include abnormalities on structural neuro-imaging, cognition (impairment in attention), eye tracking, event related potentials and minor physical abnormalities, traits that are apart from last mentioned appear to normally be under genetic control (e.g. twin studies).<sup>26-28</sup>

### Conclusion

Much of the current research-work in to biological basis of mental disorders is predicted on implicit concept of disease - that is less critical and sophisticated as it should be. However conceptualization of mental illnesses in the early part of last century was conscious of this dilemma. We find a useful reminder in Jasper's dictum that, in psychiatry, "the idea of the disease entity is in truth an idea in Kant's philosophical sense...the concept of an objective which cannot reach...but all the same it indicates the path for fruitful research and supplies a valid point of orientation for particular empirical investigation".<sup>6</sup>

Reviewing the work of Kraepelin, one comes to the conclusion that he was anything but dogmatic in his view - unlike Sigmund Freud. He also had the intellectual integrity to accept many of the arguments of his critics. In one of this last articles, "Pattern of mental disorders", Kraepelin (1920) took a radical departure from his earlier views, stating that "it is natural to turn away from arranging illnesses in orderly well-defined groups and to set ourselves instead the undoubtedly higher and more satisfying goal of understanding their essential structure". No summary could do justice to this profound reflection on the cardinal conceptual issue of psychiatry.

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