Schizophrenia

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It is more than one hundred years, in 1896 Emil Kraeplin divided the broad class of functional psychoses into two groups on the basis of eventual outcome. They were manic-depressive insanity and dementia praecox.

The predominant symptoms of manic depressive insanity were affective features, fluctuating course with frequent relapses and full recovery between episodes. Dementia praecox (the term first used by Morel in 1856) included catatonia described by Kahlbaum (1874), hebephrenia of Hecker (1871) and Kraeplin’s own dementia paranoïdes. The clinical syndrome represented a disease of brain, which pursued a steady down hill course to a state of chronic impairment of ‘intellectual’ functions or at best partial recovery. Kraeplin’s concept included weakening of emotional activities and loss of inner integration of cognition, emotion and volition- the intrapsychic ataxia

Then Eugene Bleuler under the influence of the powerful psychodynamic schools took us on a longer detour, enriching in many ways but riot without an apt comment by Roti and Harvey “to have forgotten that schizophrenia is a brain disease will go down as one of the great aberration of the 20th century medicine”.

Eugene Bleuler published his dementia praecox or the group of schizophrenias in 1911. Bleuler disagreed with the cognitive arid intellectual impairment and considered them as associational defect and essentially the disorder was viewed as psychological rather than neuropathological. He renamed dementia praecox as schizophrenia and divided the symptoms complex into Fundamental or primary and Accessory or secondary. The primary symptoms were disturbance of association (thought disorder, and loosening of association), affect, autism and ambivalence. The secondary symptoms were hallucinations and delusion.

Bleuler’s emphasis on fundamental symptoms, not necessarily psychotic features, lead him to include his own sub-category, the simple schizophrenia. This then opened the gates to ‘include riiild arid latent’ cases to the limit of absurdity. To quote him ‘the simple schizophrenia vegetate as day labourers, peddlers and even as servants. They are also vagabonds arid hoboes On the higher level of society the most common type is wife who is unbearable, constantly scolding, nagging. always making demands, but never recogniziiig duties’

Kasanin in 1933 introduced the concept of schizoaffective disorder, to the relief of clinicians but further broadening the boundaries of schizophrenia. Kurt Schnieder in 1959 produced a set of criteria he called First Rank symptoms (FRS) where hallucination and delusions (the Bleuler’s accessory symptoms) featured prominently. They were considered pathognomonic in the absence of disturbance of memory, orientation or delirium. The all important outcome remained immaterial. While Europe (except Swiss group) remained orthodox, the United States under the influence of psychoanalytic schools, schizophrenia became the most favourite diagnosis, accommodating anything which did not fit anywhere. Then a time came when such diagnostic pattern was felt to “compromise treatment selection and still worse research efforts”.

New Diagnostic Criteria

Feighner et al in 1972 quietly developed a research criteria for the diagnosis of schizophrenia which required a six months duration of illness, objective signs and symptoms and specific inclusion arid exclusion criteria.

Soon two multinational studies in early seventies became a land mark in exposing the anarchy in the diagnosis of schizophrenia and paving the way to objectify the symptoms complex (rather than so called aetiological basis of DSM II). They were John Cooper’s (1972) Psychiatric Diagnosis in New
York and London and WHO International Pilot Project on Schizophrenia (IPPS). This was followed by attempts at developing more objective tools like DSM III and IV of American Psychiatric Association and ICD 9 and 10 of World Health Organization.

Crow in 1980\(^8\) basing his argument on molecular pathology and symptoms complex, postulated schizophrenia as more than one disease. It seems two syndromes can be distinguished - the first. Type I equivalent to ‘acute schizophrenia’ characterized by positive symptoms like delusion, hallucination and thought disorder. (seen in early years and settle down with neuroleptics); the second type II equivalent to ‘defect state and characterized by negative symptoms like affective flattening, poverty of speech and cognitive deficits in pre-morbid development and less favourable response to neuroleptics.

Liddle\(^9\) has further subdivided schizophrenia into three categories and some evidence is available from functional imaging techniques (cerebral blood flow). They are: (1) reality distortion syndrome (abnormalities in medial temporal lobe); (2) dis-organization syndrome (dysfunction of right ventral prefrontal cortex) and (3) psychomotor poverty syndrome (dysfunction of left dorsal prefrontal cortex).

**Neuroleptic Drugs and Neurotransmitter Research**

In 1952 Delay and Deniker\(^10\) introduced chlorpromazine not as a super sedative but as a anti-psychotic. Soon after, neuroleptics found a place in psychiatric practice. It was suggested that the anti-psychotic properties of these drugs were related to their ability to induce extra pyramidal side effects\(^11\). The work of Hornykiewicz\(^12\) (1973) established that dopamine was depleted in the brains of patients who had parkinson’s disease. Carlsson and Lindqvist in 1963\(^13\) described selective effects of neuroleptic drugs on central dopamine turnover and attributed it to dopamine receptor blockade.

The discovery by Kebabian et al\(^14\) (1972) that dopamine rich areas of brain contained a dopamine stimulated adenylate cyclase allowed testing of the “dopamine hypothesis” in vitro. Phenothiazines and thioxanthenes blocks adrenelate cyclase. But an important group of drugs. the butyrophenones (haloperidol) did not fit into this model. An alternative approach to the dopamine receptor is by the use of ligand-binding procedures. The receptor, which are assessed by this system, form a second and separate class of dopamine receptor D2. They are not linked to stimulation of adenylate cyclase activity.

Our understanding of dopaminergic function in the brain has been enhanced by molecular cloning of subtypes of dopamine receptor. The sub types include D1 and D2, together with three new receptors. In 1990. Sokoloff et al\(^15\) identified D3, Vantol et al\(^16\) and Sunahara et al in 1991\(^17\) identified D4 and D5 receptors.

In 1989 Carlsson\(^18\) maintained that dopamine hypothesis rest eventually on indirect evidence and even this is not satisfactory as anti-dopaminergic agents are not always efficacious in schizophrenia. Also that synptomatology is mimicked not only by dopamine agonist but also by PCP (phencyclidine) and anti glutarnatergic agents. Carlsson depleted dopamine by reserpine and the immobility thus achieved was dramatically reversed by systemic treatment with NMDA receptor antagonist. This still remains unexplained. It may be dopamine dysregulation rather than hyperdopaminergia. Their blockade could facilitates other activity.

Clozapine and risperidone have shown the place of serotonin (HT2) adrenergic (Al) and histaminergic (HI) activity. But the progress in this direction has not yet helped to understand the mechanism which produce the clinical picture.

**Structural Basis**

In recent years the hypothesis that schizophrenia is a brain disease has significantly gained ground. Structural imaging of the brain in life dates back to Dandy’s\(^19\) introduction of pneumoencephalography in 1919. in 1927 Jacobi and Winkler\(^20\) claimed that 18 of 19 schizophrenia patients showed ‘unquestionable’ internal hydrocephalus. But pneumoencephalography is a procedure which can cause serious side effects in certain situation. In 1929 the American Roentgen Ray Society declared that it
was unethical to use normal controls in pneumoencephalographic studies though the results were strongly supporting the view that was a biological basis for schizophrenia. The invention of computer-assisted tomography by Hounsfield\textsuperscript{21} in 1973 represented a major advance in the investigation of the structure of living brain.

**A. Computer Assisted Tomography in Schizophrenia**

A large number of CAT scan studies on brain have shown abnormalities in schizophrenia during the last two decades. The most robust findings of CAT studies are:

- **Ventricular enlargement (lateral and third ventricles), cortical atrophy (increased sulcal markings)**
- **Cerebellar vermin atrophy and reduction in cortical volume involving gray matter.**

**Lateral Ventricular Enlargement:** The first study of CT scan abnormalities in schizophrenia was published by Johnstone et al in 1976 and 1978\textsuperscript{22,23}. They reported a significant enlargement in the area of lateral ventricles in a group of chronic institutionalized inane schizophrenics as compared with a group of age matched normal controls. Andreasen et al\textsuperscript{24} noted that 36 out of 49 further studies which compared schizophrenic patients and controls under blind conditions found some increase in lateral ventricular size.

Since then more than 90 controlled studies of ventricular size in schizophrenia have appeared in literature\textsuperscript{25-28}. Ventricular dilatation has been demonstrated in patients early in the course of the illness\textsuperscript{29,30}. Most though not all studies have found a non-progression of ventricular size on follow up\textsuperscript{31-32}. Taken together these results suggest that ventricular dilatation is present early in the course of illness and is static.

**Third Ventricle Enlargement:** In a review and meta analysis of 23 studies Raz and Raz\textsuperscript{25} noted that in most studies, third ventricle enlargement was demonstrated despite the small size of the structure. In twin studies, Reveley et al (1982)\textsuperscript{33} compared ventricular size in series of identical twins who were discordant for schizophrenia using C.T. scans. Schizophrenic twins had larger ventricles than their co-twins in 6 out of 7 cases.

Pamnani and Ahmed\textsuperscript{34} and Ali\textsuperscript{35} in Pakistani samples of schizophrenics found statistically significant increase in VBR. Pamnani found that VBR in mixed schizophrenics group (with negative symptoms) was twice the size of controls than schizophrenics with positive symptoms. No difference was found on the basis of duration of illness or length or treatment.

**B. Magnetic Resonance Imaging (M.R.I)**

This structural imaging technique is superior to C.T. scanning in its ability to differentiate gray and white matter. With M.R.I., visualization of temporal lobe and cortical sulci is much superior. Studies using M.R.I. have been carried out on schizophrenic patients since 1983.

In 1988, Crow\textsuperscript{36}, confirmed increased size of lateral ventricles which became more prominent posteriorly. M.R.I. studies will be reviewed under three categories.

a) **Assessment of whole brain size in schizophrenia:** Several studies have found a reduction in brain area/volume in schizophrenic patients as compared to controls. The magnitude of this reduction is about 3-5%\textsuperscript{37-41}. The overall decrease in cerebral volume was found to be more in the gray matter as compared to white\textsuperscript{42}.

b) **Twin Studies:** Twin studies show that schizophrenic twins had larger ventricles that their co-twins\textsuperscript{33,43}.

c) **Temporal lobe Abnormalities:** M.R.I. studies have been consistently demonstrating that schizophrenics show gross or localized changes of temporal lobe\textsuperscript{44}. A few studies have reported significant reduction of left temporal areas as compared to the right side in schizophrenic patients\textsuperscript{45-49}. With M.R.I., it has been found that structural changes are even before the onset of disease and that it is non progressive. How ever, in a recent study by Jacobsen et al (1998)\textsuperscript{50} through anatomic brain
magnetic resonance imaging scan have shown that progressive reduction of temporal structure occur with ongoing illness in childhood-onset schizophrenia. Also that it is right temporal involvement then left.

C. Functional Imaging
A) Hypofrontality: Functional imaging was first applied to schizophrenia by Ingvar and Franzer in 1974. By using this techniques to measure regional cerebral blood flow, they found that schizophrenic patients had relatively lower activity in regions of frontal cortex that normal subject and now known as hypofrontality. Functional neuroimaging studies of schizophrenia reports two forms of hypofrontality:

1. Reduced prefrontal blood flow and metabolism in people with schizophrenia at rest.
2. Relative failure of activation of prefrontal cortex (relative to rest), when patients perform cognitive tasks.

a) Review of Positron Emission Tomography (PET) studies has largely supported the findings of hypofrontality in schizophrenia.

b) Receptor Distribution: Basic research has provided strong evidence that the mechanism of action of neuroleptic agents is by blockade of the D2 dopamine receptors. The D2 receptor occupancy by neuroleptics is estimated by comparing the extent of reduction of radioactive D2 receptor ligand binding in the striatum of patients on neuroleptics as compared to drug-free controls. Various investigators have demonstrated that patients on chronic neuroleptics show 65-80% receptor occupancy. This level of occupancy probably corresponds with clinical efficacy. Atypical neuroleptics also show striatal receptor occupancies (does not spare striatal D2 receptors). New Approaches: Through proton MRI studies it was possible to show that never treated schizophrenics show a significant increase in glutamine level in medical frontal cortex as compared to controls. An interesting new technique called diffusion tensor imaging is used to study direct assessment of large axon masses stretching from prefrontal cortex to striatum.

Other Significant Contribution

Genes: The causes of schizophrenic illness remains obscure. A genetic contribution is widely accepted. Evidence from twin family with adoption studies argues persuasively that genetic features play a strong aetiological role in schizophrenia. But the fact that the onset of symptoms is often in adult life and the concordance in monozygotic twins (about 50%) falls short of 100% suggest that genes may be relevant only in predisposing to some other factors.

Obstetric Complications: Obstetric complications are increasingly recognized to represent an important somatic environmental factor associated with the later development of schizophrenia. Many studies have shown that obstetric complications are commoner in early on set schizophrenia and in chronic schizophrenic subject than in controls. Acute, late onset and female schizophrenic subjects do not seem to share the excess of obstetric complications. This may be one reasons that all studies do not show an association with obstetric complications. Four most recent studies suggest that the incidence of obstetrics complications is higher in people with schizophrenia but the magnitude is much less than the 2:1 excess indicated by the earlier literature summarized by Geddes and Lawrie. Maternal influenza: One of the most consistent epidemiological findings in psychiatry has been that people with schizophrenia are more likely to be born in the late winter and spring months. The more obvious explanation is exposure to viral infection in utero, for many viral infections are commoner in winter. Mednick et al examined the effect of the pandemic of ‘Asian flu which occurred in Helsinki in the autumn of 1957. It was seen that several months after the influenza epidemic (in spring 1958), there was 88% increase in the births of people who subsequently were diagnosed as schizophrenics.

**Polio Virus:** It has been suggested that prenatal infection with polio virus, an entero virus, contributes to the development of schizophrenia because a decline in the incidence of schizophrenia occurred in many countries after the introduction of polio vaccination.81,82.

**Pre-morbid Abnormality:** Neuro-developmental abnormalities in the pre-schizophrenic persons have repeatedly been described and is well established that early signs of the disorder can be found during infancy.83.

(a) **Deviancy as children:** Higher proportion of male preschizophrenia children have had history of deviancy in childhood.

(b) **Premorbid IQ deficit:** is uncommon in preschizophrenic girls. but appears to be more pronounced characteristics of pre-schizophrenic boys.

(e) **Abnormal Personality:** Forester et al in 199184,85 have noticed personality problems and difficult social adjustment in 40% schizophrenics.

(d) **Childhood characteristics:** Jones et al (1994)86 examined 4746 children born during one week in 1946. Those who later became schizophrenic were slower to pass their developmental milestone that normal, were more likely to play alone at the age of four years and showed poorer performance on verbal and non verbal tests at the age of eight.

(e) **Posture and Movement:** Walker (1993)87 examined home movies of pre-schizophrenic children and compared it with movies of normal children. The pre-schizophrenics showed more postural and movements abnormalities of upper limbs, particulark during the first two years.

(f) **Pruning process:** Feinberg in 198388 pointed out that the normal process of’ pruning of cortical synapses continues throughout adolescence, and that an abnormality of pruning of dopamine synapses may be critical to the development of psychotic symptoms.

(g) **Laterality:** There is growing evidence that schizophrenia is associated with left side brain pathology. Flor Henry (1969)89 was the first one to suggest that temporal lobe epilepsy was more commonly associated when the focus was left sided. Several recent studies have suggested left side volume deficits of structures, such as planum temporale, which are thought to play a role in language90.

(h) Birth weight and head circumference have been found to be significantly smaller in relation to the length. which is particularly evident in female pre-schizophrenic newborns.73,74,91,92.

**Social and Family Factors in Relapse**

Brown and Birely in 196893 suggested that the recurrence of schizophrenia symptoms is preceded to an unexpected degree by the occurrence of life events three weeks before admission. Relapse was more likely where expressed emotions (EE) were high amongst the relation which includes over involvement, hostility and critical comments on the part of relatives.94-98. Bateson et al (1956) originated the idea of ‘double bind’ which is a disordered family communication. Here conflicting parental messages are given through behaviour, attitude and feelings. This abnormal social interaction is postulated to be a contributing factor in schizophrenia.99.

The change of term dementia praecox to schizophrenia, opened many new areas of observation and investigation. Type 1 and type II schizophrenia is a step further in the understanding of this complex disorder. In the wake of new tools and sophisticated methodology, is it time to change the term once again or break the unitary concept and identify different diseases? It may not be too far away.

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