PSYCHOSIS IN RELATION TO EPILEPSY - A CLINICAL MODEL OF NEURO - PSYCHIATRY

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ABSTRACT

Psychosis occurring in epileptics has always been an area of research interest, particularly, because of possible link of mental illness, organic lesions, convulsive process and behavioural abnormality, all occurring together in the same subject. Vast amount of investigation on this subject has been done with a view to understand something more fundamental in 'Brain-Behaviour Connection'. Occurrence of interictal phase of psychosis long after cessation of seizure has driven investigators to conclude the two being unrelated, which has brought important issues of brain pathology and behavioural abnormality into focus of research from dimensions of genetics, neuroendocrine and environmental influences. The aspects of behavioural neurology, behavioural genetics, genetics of epilepsy and 'shared common genetic diathesis for development of psychosis, possibly converge in the neuropsychiatric model of 'psychosis in relation to epilepsy'. E.E.G. - spiking and regional slow waves in inter - ictal phase are emerging as correlates determining behaviour. Status of prolactin - dopamine relationship and its correlation to neuro - cognition may be another pointer in guiding some of these complex issues. It is expected that current focus of research should be able to develop on the profile of 'psychotic brain' also. One of the major clinical issue is identifying epileptic subjects prone to develop psychosis with precision of nature and type, not only because such developments jeopardises and compromises the state of art treatment done for epilepsy, but also because of devastating deterioration in quality of life of patients and relatives, besides having pharmacoeconomic devaluations. Studies have revealed that more detailed work up in the beginning may possibly identify high risk groups based upon clinical phenomenology, E.E.G. topography, endocrine status, regional brain damage, etc.

The presentation attempts to focus some of the relevant clinical issues with reference to a particular comparative study of psychosis in epilepsy and functional psychosis (schizophrenia) to understand co-existence of divergent clinical conditions.

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PSYCHOSIS IN RELATION TO EPILEPSY

Mr. Chairperson,

It is a matter of great honour for me having the opportunity to deliver this oration today. I am thankful to the Indian Psychiatric Society for providing such a privilege to me. I hope the context, content and the focus in my lecture is able to maintain the scientific psychiatric rhythm that has been prevalent on the platform of the Indian Psychiatric Society.

I dedicate this oration to my teachers, particularly my teachers of basic sciences in pre-medical education and all those who have taken pains, struggled and devoted their valuable energy and have taken extraordinary efforts in training me as a person being able to handle the issues of human suffering. It has not been easy for a person of my background, but at every turn I found someone or other to guide me and show me the path to study the scientific aspects of human behaviour.

Psychiatric illness has been a complex area for understanding. The pendulum for definite evidence of etiopathology has been swinging between various disciplines. However the brain has always been the prime focus of attention. By and large psychiatry has always suffered controversy. Concepts of dichotomies have dominated. Complexities of mind and matter have been areas of great concern to preserve and pursue human civilization since time immemorial.

Behaviour is intimately linked with the brain and delineation of such a link has wider implications for designing therapeutic strategies to cope up with the hurdles of positive mental health.

Research on this connection has been complicated because of various influences-some within control and some outside our control. However, the need for a clear model to study this aspect is obvious. Experimental models have limitations of extrapolating the findings with humans. Epilepsy - which means - "Possession from outside" is one of the situations which can throw some light on this aspect.

Adolf Mayer's 'psychobiology' found undoubted concurrence. For about two centuries scientists in medicine of behaviour kept believing and handling clinical problems considering the factors outside the realm of human anatomy and physiology. I shall discuss the relevance of clinical model of psychiatric disease with particular examples of psychosis in relation to epilepsy. During the talk I will briefly touch upon need and implications of such models, avenue of research on psychotic brain in epilepsy, an update and risk factors in interictal psychosis. I will draw the references from some of our studies in this area and detail on a particular prospective study done during last 6 years and like to invite your attention to the implication of the findings for aetiopathology, management and prevention of mental illness and finally discuss the future direction of research in this area.

Research on interictal psychosis is expected to give some clue to the patient question on brain behaviour connections.

Epilepsy, as a disease has its reference and detailed description from vedic period. Ancient Indian literatures have detailed accounts of epilepsy. In vedas four types of this disease, along with details of auras, delusions and hallucinations have been described. Further, both epilepsy and psychosis in epilepsy have been described in Ayurveda. Charak Sanhita has not only given description of the disease but also given a well written document of treatment and precaution.

Some of the naturally occurring clinical syndromes provide excellent opportunity to study brain - behaviour connections e.g. mental retardation, endocrinal diseases, vascular brain diseases, etc.

Epilepsy - the sacred disease fits well in the description of such a model for exploring the complex field of neuropsychiatry because -

1. It has demonstrable brain lesion
2. There is a high degree of psychiatric propensity.
3. It has a wide range of psychiatric
4. There is a well defined natural course of development of events in the same subjects. The association of epilepsy and madness has been a strong one, known to mankind since sixteenth century. History of epilepsy has close association to history of psychiatry. Both have been referred to be associated with demons and witchcraft and supernatural suffix. Hippocrates gave first medical text and brain was thus the seat of both epilepsy and mental illness. Relationship between moon, epilepsy and madness was highlighted by gospels and it still prevails in some form or the other. Romans called it 'morbidus lunatics' - person who committed sin against moon. The term lunatic embraced period affliction of brain, including epilepsy. Arabs called it the diviners disease and described it as associated with prophetic powers.

In eighteenth century first substantial treatise was published by Tissot in 1770, and the influence of moon continued. During seventeenth and eighteenth century, it used to be an asylum diagnosis and patients were chained like psychotics. It was during nineteenth century that the disease was delinked from these aspects. Pinel with William Tuke and Connoly, are credited for unchaining these patients. Esquirol, Morel, Falret, Sieveking have been remarkable in this field. Hugling Jackson gave the first detailed account of epilepsy and psychosis. Maudsely gave the concept of masked epilepsy.

The prevailing concept of neuropsychiatry of epilepsy has been investigated in last 20-30 years, particularly after advancement in the field of neuroradiology and neurochemistry. The model of epilepsy of psychosis is the most appropriate clinical model of neuropsychiatry of behaviour to further the study of possible origin and neurobiological basis of a range of emotions and behaviour, particularly, the event of interictal psychosis. Once we understand the inter-ictal psychoses which is in controversy for being related to brain damage, it may be possible to extrapolate the findings and develop a clear biological model in general. The body of knowledge of psychosis in epilepsy today has all the ingredients which the so called functional psychosis has also been described to possess.

Regional brain function versus whole brain function is a key issue today after obtaining massive scientific data. Though attempts have been made to find out discrete areas of brain dysfunction, it is becoming increasingly clear that function of various subsystems of brain, whether measured electronically, chemically or by imaging is interdependent and simultaneous, thus bringing disorders of various regions to the state of merely syndromes and not diseases, I wonder how worthy is to search for isolated discrete regional brain dysfunction, especially in the field of behavioural medicine. Localization is being done at the expense of functioning of brain in totality and in the process one syndrome is treated and the other appears and remains unrecognized and untreated. It happens in epilepsy to suicide, it happens in stroke and in Parkinsons Disease. Neurologist's teaching of localization is partial teaching. It does not consider the suffering, reaction and expression of the healthy part of the brain. The results are obvious, disability and poor quality of life in these subjects. Seizure remission can never be the sole aim in the treatment of epilepsy.

Presence of epilepsy, that too with a strong genetic component in the humans is itself a matter of investigations as to whether there is a purpose. We know that hippocampus has lowest seizure threshold. Inherent, universal low seizure threshold of hippocampus indicates seizure as 'protective mechanisms' for behavioural abnormalities. But for the convulsions through excitation of hippocampus the wave and spikes travelling from various focal epileptogenic areas, possibly there would have been only psychotic subjects not epileptics considering the link of seizure and psychosis and thus probably the name "the sacred disease". Maudsley (1874) described epileptic mania as most dangerous form of insanity and also accepted the concept 'masked
epilepsy' and that change of character and temperament could occur months and even years before distinctly epileptic seizure would manifest. Our technical limitation, ethical boundaries, clinical urgency, indirect benefits and high cost in brain research is keeping us frustratingly distant to develop a clear model of brain and behaviour in health and disease.

Such limitations have increased favours with neurochemical studies and illuded us to derive indirect conclusion of normal brain functioning.

The insanity psychosis has high prevalence reported to be 10% and as high as 50% depending upon treatment setting. Schizophrenia in epilepsy has been particularly reported to be higher in prevalence from mental hospital set ups. The interval between onset of epilepsy and onset of psychosis has been reported to be 11 to 22 years with mean of 15 years. It is evident that considerable number of years required for a patient to live with epilepsy in order to develop psychosis. Development of psychosis occurs more than 5-8 years after last fit. Occurrence of psychotic symptoms long after clinical and electrophysiological remission of seizures opens up clear vistas of scientific investigations drawing the conclusion of the association of the two. Why does the brain choose to go psychotic after a considerable number of years have lapsed? This needs answer to the two fundamental issues 1- Were the interictal period really free from neurobehavioural and neurocognitive disturbances, 2- Are the two unrelated?

Intensive work in this area have remained inconclusive. Most investigators believe that the two are related with a few identified controversial factors responsible for such developments such as prolonged use of antiepileptic drug, brain damage due to repeated seizures, kindling, particular seizure - type focus of origin and direction of spread of neuronal excitation. Others have clearly and conveniently ignored such factors and almost drawn a conclusion that the two are not related and are clinically independent of each other, using the data of time gap as primary support in their argument, to the extent that theory and possibility of group heterogeneity and genetic vulnerability of epileptics has also been discussed with strong argument delineating characteristics of those who develop psychosis against those who do not.

The first question of symptom free interictal period has been much less clear than the question of investigation of possible link between psychoses and epilepsy, primarily because of difficulties in methodology and obtaining reliable objective data. Investigating interictal psychosis may have far reaching conclusions for not only treating abnormal behaviour, but also in modulating, improving and shaping behaviour biologically which is chemically mediated and chemically manured also, thus providing impetus to 'Behavioural Engineering'.

The psychological abnormality and cognitive effects which appear associated with epilepsy whether complex partial or primarily generalised, are not the events of clinical surprises any way because the whole brain goes into not only electrophysiological turmoil but also in neuro-chemical, neurohumoral and neurocognitive dysregulation, and therefore appearance of behavioural and psychological components, in whatever severity, are inherent and in built into the 'seizure'. Simply their recognisability is a matter of clinical acumen and precision.

Similarly, subclinical seizures are primarily manifested in a range of borderline neuropsychological symptoms associated with or without EEG abnormality. It is difficult to comprehend 5-7% abnormal EEG in population distribution without correlating brain dysfunction symptoms. Almost a similar degree of EEG abnormality in psychiatric patient population is also an evidence of connection of electro physiological abnormality to psychological symptoms. Conversely 30-40% EEG negative clinical epilepsies are not free from behavioural and subtle neurocognitive signs and symptoms.
It appears that a different neurobiological substrate may be responsible for development of psychoses in relation to epilepsy. This psychoses is different than functional psychoses on almost all clinical and laboratory parameters. However this may itself be heterogeneous and composed of various subgroups of which at least two being most prominent:

1. Psychoses with more left temporal abnormality and
2. Psychoses related to left temporal complex partial seizures.

With advancement of neuroimaging functional anatomy of psychiatric disorders is getting established, regional and discrete brain involvement have been confirmed in both schizophrenic and affective psychoses. Regional brain focus in primary epileptics have also been investigated with high degree of reliability to the extent that the term ‘idiopathic epilepsy’ is on its way out. MRI studies in primary epilepsy have confirmed some or the other regional brain affection in majority of cases.

When we match these two sets of neuroimaging data, strange inter-relationship emerges:

1. What is the incidence of common site of regional brain affection in functional psychoses and epilepsy?
2. Is it possible to identify, predict and modify the treatment of epileptic subjects vulnerable to develop psychoses? Psychosocial deterioration, occupational loss, incidence of suicide and overall deterioration in quality of life of epileptics due to development of psychotic process needs to be looked into and require clinical readressal. There have been attempts at some centres to record in-depth activity and relationship of paroxysmal disorder of behaviour with seizure within brain, particularly non progressive spike and wave activity.

**FORCED NORMALISATION**

Landolt (1958) said - "talking more crudely, there would seem to be epileptics who must have a pathological EEG in order to be mentally sane "while commenting on forced normalization.

Concept of conversion was stated by Ferriar in 1795, hundred years before Sigmund Freud, stated - "a disease is said to be converted, when new symptoms arise in its progress, which require a different designation and which either puts a period to original disorder, or combining with it, alters the physician’s view reflecting the prognostics, or the method of cure”. Several authors used epidemiological data on prevalence of epilepsy in schizophrenia and vice versa but it could not be found more than what is seen in the general population. The issue of convulsive therapy, forced normalization and alternative psychosis are complex and clearly mutually exclusive to explain the relationship of psychosis to epilepsy. There is a case of biological antagonism noted by Meduna (1935) and Nyiron & Jablonsky (1930). However more recent studies also indicate possibility of co-existence or comorbidity model. Most believe that the two are manifestations of the same brain disease. There is no antagonism between epilepsy and schizophrenia but between symptoms, namely seizures and psychosis. This is compatible with the view that in combination of epilepsy and schizophrenia an alternating relationship is the rule. However, it is the questioned syndrome antagonism of basic disorder.

Number of clinical psychiatric syndromes are related to preictal, ictal and postical phases and it is impossible to examine the issue in mutual exclusion. Indeed neither epilepsy nor schizophrenia can be viewed as diseases, they are both symptoms of several underlying disease, some of which seem common to both. It is often dened that forced normalization and its clinical counterpart, alternative psychosis, occurs probably with good reason.

**COGNITION AND LIMBIC SYSTEM**

Though it is clear that agonists like L dopa, apomorphine and normifensin can in
crease psychotic tendency in biologically vulnerable subject and dopamine agonists like phenothiazines and butyrophenones can induce a seizure, the issue of bioamine antagonism is not independent of other various neurochemical operations. In a specific subgroup only such clear-cut antagonisms are possible. The issue of neurotransmitter antagonism gains much relevance in medically and neurologically complicated subjects for management. Recent advent in gabaminergic and glumatic acid influence on dopamine system may add valuable knowledge. Another subject of relevance is neurological findings like hard and soft neurological signs and their neurotransmitter expressivity. An excess of sinistrality has been widely reported in psychosis and epilepsy. However there is no correlation to type of psychosis available.

Limbic brain structure and function has undergone a major research exercise from the field of neuroimaging, neurochemistry and electrophysiology. Neuroanatomy has been extensively studied. However the clinical implications of the information is yet to be confirmed irrefutably. The three parts amygdala, septum, thalamocingulate gyrus have separate as well as conjoined function to perform. Experiments indicate that these structures are primarily responsible for human psychological factors like emotion and motivation. It has been brought out that intactness of these three is prerequisite for organisation and control of mood, sexual behaviour and visual perception.

Other behavioural functions are also governed by these but it is not quite clear whether discrete areas are solely responsible structures. Much of the functions are performed by wholeness. Relationship of aggression to amygdala has also undergone tremendous research, particularly in experimental psychology area. Whether these will have direct or indirect clinical implications is a feature for tomorrow.

Kindling has been shown to be associated with the entire range of psychological process occurring in epilepsy. Whether kindling is a universal phenomenon or it is also selective in genetic sub-group has not been worked out. How much this electrochemical event is able to sensitise D2 receptor and increase its binding to give rise to behavioural component of epilepsy is not known. However, it is certain that in a section of patients, electrophysiology and neurochemistry intermingle. It is no doubt the strongest experimental model of behavioral syndrome in epilepsy.

Cognitive impairment has been an area of clinical concern in epilepsy, so has been the component of depression. We tried to investigate depression linked cognition in primary generalised epilepsy and its clinical correlates and therapeutic intervention (1993). It was hypothesised that depression and cognition in epilepsy have some kind of interrelationship. Hippocrates described melancholics ordinarily become epileptic and epileptics become melancholic.

Recently mood disorders have also been described to have neurocognitive changes demonstrable by clinical as well as psychometric tests and it has been found that this impairment recovers with treatment of depression. We carried out the clinical study and it was observed that cognitive impairment was present in majority of primary epileptics. It was found that the cognitive dysfunction in memory and intelligence is 'depression linked'. Depression was also prevalent in the population.

Statistically significant correlation was observed between W.M.S., I.Q. and H.D.R.S. suggesting that the reported cognitive impairment does not necessarily exclude depression. It appears that most of the epileptics with mental impairment have in fact depression which could be efficiently treated.

The study draws attention to the fact of implication for reducing mental morbidity in epileptics and to improve overall quality of life.

In one of our old studies we tried to categorise E.E.G. abnormality in psychiatric subjects. Biorythmic and biochemical factors have obvious influence on clinical signs. It was identified that these electrophysiological changes cor-
relate with symptomatology. Understanding that physiological changes preceed pathological, it was thought that psychophysiological changes may preceed psychopathological changes.

From a series of psychiatric subjects, on analysis, we found four types of abnormalities
1. Unusual slow rhythm in awake state
2. Focal abnormalities
3. Bilateral frontal and bilateral temporal abnormalities
4. Generalised bursts of sharp wave activity.

Recently, we tried to explore the issue of biological antagonism in convulsion and psychosis by questioning whether anticonvulsants change the efficacy of E.C.T. In a controlled study we found that although carbamezapine is an established antiepileptic drug, its concurrent use does not affect the efficacy of E.C.T. Addition of carbamazepine in one group did not affect the global recovery. It may be possible that there are different mechanisms for anticonvulsants, antiepileptic and E.C.T. at neuronal levels. Much talked about subject of cognition, schizophrenia and E.C.T. was studied by us and in a small sample of subjects. We found that the mean number of modified electroconvulsive therapy in schizophrenia is not associated with cognitive dysfunction.

I now invite your attention to studies pertaining to psychosis in relation to epilepsy.

In this connection I will briefly make reference to the study conducted by us in Bombay over last ten years and a particular study started in 1988. It was hypothesized that in case of psychoses relation to epilepsy,
1. a functional topography is possible.
2. that psychoses in epilepsy is related and not independent.
3. seizure control is not always directly related or protective for development of psychoses, and
4. it is possible to identify high risk groups.

Index group of psychoses with epilepsy was compared with epileptics. (without evidence of psychosis and functional psychoses) and non epileptics. All subjects were adults, clear evidence of normal behaviour between onset of behavioural changes and last fit. R.D.C. criteria was used for defining psychoses. The assessment was done on clinical, psychopathological, electrophysiological, neuropsychological parameters in all the subjects. Baseline serum prolactin in 30 index and 30 control group, serum cortisol in 20 subjects each, SPECT in twelve - index subjects, CT scan in 34 index and 30 control and MRI in index group subjects was performed. Treatment design was restricted to use of antiepileptic - carbamezapine and neuroleptics (haloperidol) and no use of E.C.T. Besides conventional psychopathological measurement in all 278 patients EEG was recorded and analysed visually, with fixed bitemporal recording of the montages for 30 minutes.

Montages were modified and fixed with continuous bitemporal recording. Certain important observation were-
1. Males outnumbered females but mean age of females was eight years higher in the group of epilepsy with psychoses.
2. C P S had a lower representation.
3. There was no significant difference in quantitative psychopathology of epilepsy with psychosis and functional psychoses, however, qualitatively there were found to be more manic type, and intermixed with affective features. Schizophrenia like psychoses was seen less than expected.
4. Epilepsy with psychoses was more organically loaded.

On EEG analysis the index group show significantly more non epileptic EEG abnormality in the form of slow wave 4-6 htz changes, 50 mv appearing for more that 20% total recording time. These EEG changes also showed regional distribution-one subgroup showed bitemporal changes which significantly correlated with psychopathology.

Patients with manic and affective loading in index group of epilepsy with psychoses show
more changes with frontal and temporal lobes and those with schizophrenic symptoms show changes restricted to bitemporal region.

Rise of serum prolactin in both the groups with psychoses was seen but rise was less marked with psychosis with epilepsy suggesting high selective dopamine activity and possible role of tubero-infundibular-hypothalamus region.

Index group with affective symptomatology showed rise which was near normal, whereas in schizophrenia like cluster the prolactin rise pattern was almost similar to that seen in control group of schizophrenic psychoses.

Close association of prolactin level fluctuation may be of predictive value.

TC 99 HMPAO study done in selected twelve cases with assistance from Hinduja hospital showed increased attenuation of both bifrontal and bitemporal area in epilepsy with psychoses group correlating positively with affective symptomatology. The study could not be enlarged to schizophrenia like epileptic group due to economic and technical constraints. No significant difference in neurocognition emerging amongst all the three groups. However, lower performance IQ was seen in group with epilepsy and psychoses. It is difficult to point out whether the deficit existed before the onset of psychosis or not but most likely this deficit is contributed by development of psychoses because of its clear differences with non psychotic epileptic group. Alternatively combination of AED and APD may also contribute to this extent.

Subtle changes seen in frontal and temporoparietal lobes are significant and correlate positively with psychopathology and symptom cluster. Almost clear trend which emerged as a conclusion of the study showed schizophrenia like psychosis in the epilepsy has more abnormalities limited to bilateral temporal lobes while those epileptics who develop psychoses with affective symptom cluster, exhibited both frontal and temporal regional abnormality.

Whether such abnormality existed before the onset of psychiatric symptoms can be answered and possibly addressed only by long term prospective study in a comprehensive manner. But psychosis with epilepsy group clearly emerged distinct than functional schizophrenic psychosis. The study had several limitations and some of the findings appeared unsupported from literature, eg. more affective psychoses which could be explained by high incidence of suicide in epilepsy. There may well be changing trend in the phenomenology.

Serum prolactin has emerged as undisputed biological marker of a seizure episode, particularly relationship of increase in prolactin levels with time of seizure. It remains high in first three hours and then gradually declines. It indicates role of midline structures of brain in seizure, whether the spiking and clinical seizure has an 'endocrinal onset'?

It has been used to differentiate seizures from pseudoseizures. Serum prolactin also rises after experimental seizures, electroconvulsive therapy and neuroleptic medication. As a marker of tuberoinfundibular dopaminergic activity and being related to both seizure and psychoses, this particular neurohormone is likely to offer some insight into neuropsychiatric syndromes.

Prolactin, together with cortisol, and its inverse relationship to psychopathology is a fascinating area in current research field. Unfortunately alternatives to in-depth electrode recordings are not available. Such electrophysiological disturbances in deeper brain structures are also not sensitive to technical advances in EEG field. Much will depend upon electro-chemical specificity of SPECT and PET, which is yet to come.

Interictal Psychosis: The issue of psychosis interictally, however occasions considerable controversy and much of this has been explored. In order to fully understand the development of concepts related to these arguments and to explore further relationship between epilepsy and psychosis it is necessary to review even more controversial areas, namely the association be-
tween personality disorder and epilepsy.

Personality in epilepsy was recognised as "period of epileptic deterioration" and then the term "epileptic character" (by Morel) became popular. The concept regarding its development became intertwined with Freudian psychodynamics. Turner, (1907) said that, "seizure and epileptic character both are expression of same nervous constitution."

The belief was that epilepsy was a constitutional disorder in which the seizure were but one manifestation of more diverse symptomatology. Lennox (1960) forcefully made the point that patients with epilepsy were normal (psychiatically), though wide range of psychiatric disorders were reported, and that difficulties encountered were because of interactions due to complication of epilepsy.

View of psychomotor peculiarity was given by Guerrant et.al. in 1962. Gibbs and Stamps in 1953 noted that the patient's emotional reaction to his seizures, his family and his social situation are less important determinants of psychiatric disorders than the site and type of epileptic discharge. He noted that highest incidence of psychiatric disorders occurred in cases with a spike focus in this region. Most of the lesions found were in anterior temporal region, for all types of psychiatric disorders were reported, and that difficulties encountered were because of interactions due to complication of epilepsy.

Interictal psychosis has interesting phenomenology. Recent studies have established schizophrenia like psychosis from all cultures including India (Kanaka et.al 1996, Shukla et.al, 1979). These are virtually indistinguishable from purely psychiatric disorders. Hill et.al. (1957) in a most important literature brought out chronic paranoid hallucinatory states and three types were suggested.

1. Chronic psychosis with recurrent confusional episodes
2. Chronic paranoid states
3. Hebephrenic states, most usually having insidious onset with gradual progression of delusions. About two third had delusions.

Attempts have been made to correlate type psychosis and type of seizures. Evaluation has been done using PSE and Catego. Similarities as well as differences both have been noted. Non schizophrenia like psychosis, particularly paranoid and affective have also been reported.
PSYCHOIS IN RELATION TO EPILEPSY

To some extent there is direct link between certain type of epilepsy and pattern of psychosis. Comprehensive evaluation of EEG manifestationes of psychotic state occurring interictally was presented by Dongier (1959, 60). In a long series of 5,36 episodes of psychosis 44% were associated with generalised discharges, 16% were with focal discharges, the majority of those (11%) being temporal.

With regard to normalisation, disappearance of EEG abnormality was seen in 24% only, mainly of a focal or bisynchronous discharge. Over half of the cases were associated with alteration of state of consciousness and the remainder 30% showed predominantly affective disorders.

The rest showed schizophrenia like presentation or pure hallucinosis. Confusional symptoms are more frequent in patients with centroencephalic seizures; these presentations are often found associated with diffuse delta waves or more or less continuous bisynchronous spike and wave discharges on the EEG. Affective disorders were not closely associated with epilepsy type but focal epilepsies tended to show more depression-45% of T.L.E. cases compared with 24% of centroencephalic epilepsy.

Delusions were more frequent among focal epilepsies, especially where a pre-existing focal discharge disappeared. In summary, Dongier's data show differences in the presentation of psychosis between psychomotor epilepsy and generalised epilepsy, the former presented with more affective disorders and schizophrenia like or paranoid presentations. Similar data was also reported by Dorr-Zegers and Rauh (1980) emphasizing focal seizures with prolonged psychosis.

Affective psychosis per se has been rarely discussed, though several authors have found association of psychosis and epilepsy. Depression has been recognized for many years in epileptics. Symptoms like excitement, manic presentation and overactivity were present in early description of Griesinger (1857) and Morel (1860). Not much attention has been focussed on affective psychosis related to epilepsy, except the singular study of Flor-Henry's highly selective series of patients with temporal lobe epilepsy. What is clear is that affective symptoms are often intermixed with psychotic symptoms in classical schizophrenia like psychosis. Cyclic mood disturbance and bipolar disorder have been noted by Slater and Beard (1963).

Interictal Psychosis -Risk Factors. Though there is no definite data on association of identifying risk factors and prevention of psychosis in epilepsy, it is generally presumed that indentifying risk factors may affect overall quality of life of an epileptic. Some of the common risk factors from various studies are: early adolescent onset, interval between onset of seizures and onset of psychosis (14 years), female gender, complex partial and automatism seizure type, diminished seizure frequency, temporal especially left sided seizure focus, sinistrality, gangliomas, hamaratomas, forced normalisation in subgroup and mediobasal focus on EEG. None of these have been identified for definite, for development of type of psychosis.

Far more attention has been given to the interval between age of onset of epilepsy and age of onset of psychosis, which was first discussed in detail by Beard (1963). In Slater's series, the interval was significantly less for those developing hebephrenic states. The mean interval was 14 years and a correlation co-efficient of 0.48 between age of onset of epilepsy and psychosis was found. And this was given as one of the reason for aetiological relationship of epileptic seizure and psychosis.

It seems that severity of psychosis in terms of duration and outcome is inversely proportional to this duration. From one of the Scandinavian series, there is remarkable homogeneity of the interval, being 11 to 15 years. Trimble and Perez (1980) made the point that subcategories of psychosis differ and noted the significantly shorter interval in patients with nuclear schizophrenia.
The factor of mean interval has been of considerable discussion. Analysis of demography, clinical profile and hospitalisation data from many series when reanalysed has remained inconclusive, which led Taylor suggest that a "different aetiology was related to the seizure disorder in the following two groups - those who developed psychosis (had onset of epilepsy around puberty) and those who do not (had onset of epilepsy in childhood).

Gender differences of psychosis have been well known. There have been reports about organicity, differences in imaging and endocrine profile. In one of our own studies on serum prolactin, female psychotics were found to have shown significantly higher rise in prolactin levels in acute psychosis. There is an increased risk of psychosis in female epileptics. The data was further strengthened from evidence coming from temporal lobectomy. (Taylor 1975)

While acknowledging that assessment of seizure frequency is difficult, particularly, retrospectively, studies suggest that a diminished frequency of psychomotor temporal lobe seizures in patients developing psychosis. There are several reports of individual patients having antithetical relationship between seizures and psychosis which would seem to be of importance. These data suggest that there is a sub group of patients where such a relationship does hold. This may be reviewed as a form of antagonism between seizures and psychosis. A variant of phenomenon described by Landolt, as in some cases EEG is shown to normalise. Several authors have found the association of psychosis and more than one type of seizures usually with secondary generalisation from a focus.

Forced normalisation is seen in only 24% cases patients with bisynchronous spike and wave discharges were found to be generally confused. Patients having no change in EEG before and after development of psychoses showed mood swings and depression, whereas in epileptics, where discharges disappeared on development of psychosis showed paranoid features. A preponderance of temporal lobe abnormalities was shown by various workers.

Kristensen and Sindreup (1978), in a controlled study found difference in spike activity in sleep and awake study, but spheroidal recording showed highly significant differences i.e. spikes in 82% of psychotics as opposed to 41% controls, with no difference in location of temporal spikes, anterior, middle or posterior. Psychotic subjects showed higher number of independent spikes. A link was established between medial-limbic disturbance and psychosis.

It appears that psychosis in epilepsy whether close to seizure or years after, is not electrophysiologically neutral. There are EEG changes. Most probably epilepsy and psychosis represent two aspect of single brain disease, however much needs to be correlated.

Ramani and Gumanit (1982) did intensive monitoring of interictal psychosis of epilepsy, but their cases were ictally related. Perez and Trimble noted a difference in intellectual performance of their subgroup, and found nuclear schizophrenia significantly superior to the other forms. More brain damage was reported in schizophrenia like psychosis than manic depressive and affective disorders. Psychotic sample had more positive neurological signs and organicity. Psychotic subjects had more left handers or ambidextrals. Increase in sinistrality has been confirmed by many workers. However shift of dominance to alternative hemisphere was not necessary for development of psychosis.

Neuro radiology virtually revolutionised the information of interictal psychosis. Radiological studies suggest that the patients with epilepsy and psychosis probably do not differ from controls in relationship to the gross amount of ventricular dilatation seen, but CT, MRI and PET do suggest differences.

Conclusion

Future research on epilepsy and psychosis of epilepsy from pathological electrophysiological and radiological studies will
lead to greater understanding of the fascinating connection between brain and mind.

Serum prolactin has emerged as an undisputed biological marker of a seizure episode. Particular relationship of increase in prolactin levels with time of seizure i.e. it remains high in first three hours and then gradually declines, is interesting. It indicates the role of midline structures of brain in seizure, whether the spiking and clinical seizure has an 'endocrinal onset'?

It has been used to differentiate seizures from pseudoseizures. Serum prolactin also rises after experimental seizures, electroconvulsive therapy and neuroleptic medication. As a marker of tuberoinfundibular dopaminergic activity and being related to both seizure and psychoses, this particular neurohormone is likely to offer some insight into neuropsychiatric syndromes.

Prolactin together with cortisol, its inverse relationship and positive correlation to psychopathology may offer an understanding in dysphoric state of epilepsy. Regional spikes and wave and behaviour is a fascinating area in current research field. Unfortunately alternatives to in-depth electrode recording are not available. Such electrophysiological disturbances in deeper brain structures are also not sensitive to technical advances in EEG field.

Much will depend upon electro-chemical specificity of SPECT and PET, which is yet to come. With studies cited here the whole issue comes of the biological basis of behaviour i.e. what are the biological determinate, what is the neurobiology, how can we control, enhance, modulate or regulate normal and abnormal considering psychological and cultural dimensions as well.

Discussion and study of intrical psychosis may probably offer some indications to the direction into which we need to focus future research in the area of neuropsychiatry.

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**OBITUARY**

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Professor Brij Bhushan Sethi was born on 16th February 1932 in Rawalpindi. He completed his medical graduation from King George's Medical College, Lucknow in 1956 and after completing his house job in Medicine he proceeded for further studies to U.S.A. He was awarded M.Sc. Psychiatry and D.Sc. Psychiatry from Pennsylvania University and became Diplomate of American Board of Psychiatrists and Neurologists. He joined KGMC as Professor of Psychiatry in the department of Medicine in the year 1966 and became the founder and Head of the Department of Psychiatry in 1971 when it branched out from the parent department of Medicine. He single handedly developed this department into one of the biggest teaching open general hospital psychiatry units in the country. During his career he published more than 150 articles in national and international journals and was involved as Principal Investigator in more than two dozen research projects sponsored by Indian Council of Medical Research and World Health Organization. He was awarded national B.C. Roy Award for developing a speciality. He had been a very active member of the Indian Psychiatric Society and was Editor of Indian Journal of Psychiatry from 1977 till 1984. He was also chairman of various committees of the society. He took over as Principal, K.G. Medical College, Lucknow in the year 1985 and later on in 1985 became the Director of Sanjay Gandhi Post Graduate Institute of Medical Sciences at Lucknow. He expired on 8th of May 1996 due to a massive heart attack and is survived by his wife, a son and two daughters. May God rest his soul in peace.