PREFACE

Schizophrenia is a devastating neuropsychiatric disorder. Prevalence of the disorder in the general population is 1%. Its onset is generally early in life; the illness has developmental origins. It generally has a chronic course. Costs involved in its management are enormous and human suffering involved is fathomless.

The etiology of the disorder remains highly speculative. Its neuropathophysiology is only recently beginning to be understood; is heterogeneous, as is its phenomenology. This has been unfavorable to drug development for treatment. The available drugs (antipsychotics) are targeted to antagonize possibly altered receptor functions of several neurotransmitters, which may be secondary to the structural neuropathophysiology. The drugs do not effectively treat the psychopathology but treat the different symptoms in varying degrees. Some of the early antipsychotics (typical or conventional antipsychotics - typicals) effectively treat psychosis but not the recently considered core psychopathology, negative symptoms and cognitive impairment that are critical in illness outcome improvement. Also, these drugs often cause serious side effects. The recently introduced atypical antipsychotics (atypicals) seem to be effective in managing the negative symptoms, improving cognitive performance and causing only mild side effects. The long-term use of typicals, but not the atypicals, is found to impair cognitive performance and CNS cholinergic function in animals (Mahadik et al, 1998; 2001). However, stands to be proved whether the atypicals are effective against the core negative symptoms. Also, as with the typicals, the atypicals also function to alter neurotransmitter receptor functions and not the core neurostructural pathophysiology of schizophrenia. Thus, with a view to achieve development of effective as well as safe drugs for treatment of schizophrenia, there is a pressing need to understand the etiopathophysiology of the disorder.

Various pathophysiological hypotheses have been put forward to explain schizophrenia. The membrane hypothesis may be able to explain the observed neuropathophysiology and also provide a basis for evolving effective and safe treatment for schizophrenia. The "membrane hypothesis" suggests that abnormal membrane structure, that is, altered quantity and quality of various phospholipids [PLs], is prevalent in schizophrenia. Recently these changes have been considered

to be a result of altered metabolism (reduced synthesis from essential fatty acids [EFAs], and/or increased breakdown) of essential polyunsaturated fatty acids [EPUFAs]. EPUFAs are the ω-3 and ω-6 series of fatty acids that cannot be synthesized by the body and hence are essential in the diet. EFA / EPUFA intake and metabolism govern the availability of EPUFAs for PL synthesis and thus the quantity and quality of membrane PLs in both periphery and the brain (Thompson, 1992). Also, it is the EPUFA component of the PLs that determines fluidity for optimal functioning of membrane proteins and EPUFAs are second messengers for a number of neurotransmitter mediated signal transduction processes, which may account for the multi-transmitter dysfunction observed in schizophrenia. Membrane PL profile in schizophrenia is suggestive of reduced levels of EPUFAs. Accordingly, reduced membrane levels of EPUFAs are consistently reported in red blood cells and brain of chronic medicated schizophrenic patients (Vaddadi et al, 1990; Horrobin et al, 1991; Yao et al, 1994; Glen et al, 1994; Peet et al, 1995; 1996; Assies et al, 2001) and cultured skin fibroblasts from never-medicated patients at the onset of psychosis (Mahadik et al, 1994). This is known to be associated with psychopathology (Glen et al, 1994; Peet et al, 1995).

Other observations with EPUFAs and schizophrenia are also noteworthy. Better illness outcome observed in the developing countries as compared to the developed countries by the WHO (1979) during its multi-national, multi-center, epidemiological and clinical study was reported to correlate with relatively high EPUFA intake in diet (Christensen and Christensen, 1988). Peet et al (1996) have also reported a correlation (negative) between EPUFA intake and the severity of predominant symptoms. These observations strongly implicate a role for membrane EPUFAs in outcome and if proved, can have applications in management of the disorder.

It is generally accepted that schizophrenia is a neurodevelopmental disorder that may lead to dysfunction of several neurotransmitters. There is substantial evidence for the role of EPUFAs (particularly docosahexaenoic acid [DHA] and arachidonic acid [AA]) in brain development, and function as second messengers in

neurotransmitter mediated signal transduction processes. Thus the role of reduced membrane EPUFAs in etiology of schizophrenia may also be considered.

This thesis is an account of the study of the association of membrane EPUFAs with psychopathology, and thereby the clinical outcome of schizophrenia, the mechanisms responsible for the reduced membrane EPUFAs and the application of this finding. Reduced membrane EPUFAs observed in never-medicated patients in early illness, as well as the medicated schizophrenics and its association with psychopathology indicate that it may constitute or contribute to pathophysiology of the illness. Improvement in membrane EPUFA levels with concomitant improvement in psychopathology, observed with a follow-up of first-episode schizophrenic patients, add support to its role in pathophysiology and outcome of schizophrenia. When the mechanism of reduction of membrane EPUFAs, namely intake of EFAs / EPUFAs and antioxidants, and oxidative stress mediated lipid peroxidation was studied, both these factors were found to affect membrane EPUFA levels. Accordingly, supplementation with ω–3 EPUFAs and antioxidants have been considered beneficial to alleviate the psychopathology. ω–3 EPUFA supplementation regimen using low dose of the EPUFAs along with antioxidants was found to be effective in alleviating psychopathology in young patients.