S69-4
THE BIOLOGY AND THERAPY OF FIBROMYALGIA SYNDROME — OVERLAPS TO DEPRESSION

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Affective disorders including the different forms of depression are common behavioral conditions affecting mood, cognition and perception (e.g. pain). Although the efficacy of somatic therapies, e.g. with antidepressant drugs, is well established, consistent neurobiological abnormalities of etiological significance have not yet been found. One of the major reasons of this failure is the heterogeneity of the disorder resulting from different causes. Hypotheses of the etiopathogenetics are related to

1. depressiogene effects of drugs, hormones and cytokines,
2. the assumed mechanism of action of the available antidepressants. Due to the norepinephrine (NE) and serotonin (5-HT) reuptake inhibition, the major inactivating step, these neuronal transmitter systems are major targets of research. Abnormal low metabolites of NE and 5-HT are found in subgroups of patients. Additionally, altered receptors of both systems are found in post mortem brain studies. Neuroendocrine studies with agonist challenges (e.g. clonidine for α_2 receptors, apomorphine for dopamine and flenfluramine, ipsapirone and flexinoxan for 5-HT receptors) are abnormal in depressive patients. The elevated cortisol secretion and interleukin 1 and 6 secretion can be the result of stress or of hypothalamic disregulation. Altogether, there are many pathological findings of this kind, but they are not consistent in all patients, underlining the heterogeneity of the disorder.

Recent advances of diagnostic procedures, molecular genetic techniques and statistical methods revived the search for disease related genes. Most promising findings are reported in depressive patients of the bipolar types I and II, in whom a genetic component of the disease is most likely. Candidate genes linked to the above mentioned neurotransmitter abnormalities on chromosome 18 (location of a G-protein subunit) and on the X-chromosome (location of tyrosine hydroxylase) are hot spots of genetic findings. However, these results could only partially be replicated. One major bias is the insufficient definition of the phenotype which is heterogeneous. Therefore, the definition of subgroups of clinical phenotypes may be helpful in future, this can be done with clinical methodology, e.g. family history for bipolar disorders, comorbidity with anxiety or fibromyalgia and with neurobiological markers of therapy response.

S70. Schizophrenia is not a disease entity

Chairs: T Fukuda (J), H Beckmann (D)

S70-1
CLINICAL HETEROGENEITY OF SCHIZOPHRENIA: A COMMONPLACE FREQUENTLY IGNORED

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The two most widely accepted modern classificatory systems, DSM-IV and ICD-10, list 5 and 9 subtypes of schizophrenic psychoses respectively. It is our impression, however, that contemporary psychiatry, particularly psychiatric research, pays only lip service to the clinical heterogeneity of schizophrenic illnesses. A survey of three leading English-language psychiatric journals – American Journal of Psychiatry, Archives of General Psychiatry and the British Journal of Psychiatry – covering the last five years (1993–1997 incl.) has revealed that only in a fraction of studies published during this period were subjects with schizophrenia further classified according to DSM-IV or ICD-10 subtypes. Other, alternative subdivisions of schizophrenia were hardly ever mentioned nor the polydiagnostic approach proposed by Kendell was employed. A survey of the routine clinical practice in a university-affiliated teaching hospital showed that schizophrenia was diagnosed on the basis of a limited number of symptoms and, as a consequence, was seldom subtyped. Some of the main reasons for the abandonment of the nosological approach to schizophrenic psychoses particularly the depreciation of the clinical method within the context of the *Zeitgeist* of contemporary schizophrenia research will be discussed.

S70-2
THE DIFFERENT GENETIC BACKGROUND OF SCHIZOPHRENIC SUBGROUPS

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In a systematic twin study (47 same-sex pairs, 22 monozygotic and 25 dizygotic pairs) with index-twins belonging to psychoses of the "schizophrenic spectrum", we investigated twin concordance rates based on Leonhard's nosology. The results point to the existence of three genetically different groups: cycloid psychosis, unsystematic and systematic schizophrenias. In cycloid psychoses genetic loading is subordinate (probandwise concordance: monozygotic twins 39%, dizygotic pairs 31%), however, unsystematic schizophrenias are predominantly inherited (probandwise concordance: monozygotic twins 89%, dizygotic twins 25%). Monozygotic twins with a diagnosis of systematic schizophrenia have not been found, whereas 6 out of 30 psychotic dizygotic twins received a diagnosis of systematic schizophrenia. All of them were discordant for the disease.

Further, a family study on 83 probands with periodic catatonia (= clinical subtype of unsystematic schizophrenia) and 56 probands with systematic catatonia (= clinical subtype of systematic schizophrenia) resulted in significantly different morbidity risks in first-degree relatives between these diagnostic groups. In systematic catatonia, mothers had a risk of 6.8%, fathers 2%, and randomly selected siblings 3%. In periodic catatonia there was a risk of 33.7% for mothers, 15.4% for fathers and 24.4% for siblings. Fifty-nine families of the latter were multiple-afflicted with pronounced unilineal vertical transmission and anticipation, and in 10% of these families three successive generations suffered from the disease indicating a major gene effect.

Thus, it is concluded that psychoses belonging to the schizophrenic spectrum have to be divided into heterogenous subgroups of completely different genetic background.

S70-3
NEW FINDINGS IN THE AETIOLOGY OF CYCLOID PSYCHOSES

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Various studies have shown that the cycloid psychoses form a clinically homogenous, diagnostically and prognostically valid group of disorders. New findings in biological psychiatric research shed more light on aetiological and nosological considerations

and delineated distinct biological characteristics of this group of psychoses.

In a twin-study, a very similar concordance rate between monozygotic and dizygotic pairs of probands with cycloid psychoses was found, suggesting a lack of hereditary influence according to the rule of Galton. On the other hand, in mothers of patients with cycloid psychoses infectious diseases in the first trimester of gestation occured significantly more frequently than in patients with other psychoses. These infections were correlated with further obstetric complications and an early onset of the disorder. In agreement with these findings, patients with cycloid psychoses showed an increased rate of non-specific CCT-abnormalities of the brain which most likely resulted from pre- or perinatal brain damage. Neurophysiological investigations also provided specific findings. Studies of event-related potentials revealed characteristic features of amplitude and topography of the P300 in cycloid psychoses which were distinguishable from P300-alterations in schizophrenic psychoses and other psychiatric disorders. Moreover, cortical blood flow during acute phases proved to be significantly elevated in patients with cycloid psychoses, but showed no persistent abnormalities after clinical remission, especially no hypofrontality.

Altogether, these findings point to the fact that somatic influences may play an important role in the aetiology of cycloid psychoses and suggest that cycloid psychoses represent a nosologically independent entity which should be separated from affective and schizophrenic psychoses and is not identical with schizoaffective psychoses.

S70-4

ELECTROPHYSIOLOGICAL EVIDENCE FOR SUBGROUPING OF SCHIZOPHRENIA

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The current international diagnostic systems are developed based on a mixture of rationales including clinical utility and reliability of the diagnostic assessment. Monopolization of this method for the evolution of the psychiatric classification which follows practical clinical goals or even the simplicity of the diagnostic criteria instead of hypothetic ethiopathogenetical mechanisms is suspected to lead to a scientific impasse due to categories representing an amalgam of different natural disease entities. Leonhard's classification is based on clinical cross-sectional and longitudinal observations, ordered according to possible pathophysiological mechanisms, and allows to formulate testable hypothesis. In a series of studies based on 20-channel recordings of cognitive event-related potentials (ERPs), the neurophysiological differences between psychotic subgroups in Leonhard's classification and in the categories of the DSM and ICD were investigated. The P300 component of the ERPs differed between cycloid psychoses and systematic/unsystematic schizophrenia, and between these groups and manic disorders. While topographical alterations indicated deficits of left temporal lobe function in schizophrenia (Strik et al, Psychiat Res: Neuroimaging, 55: 153–166; 1993), increased P300 amplitudes were found in cycloid psychosis as a sign of a generalized increase of arousal (Strik et al, Acta Psychiat Scand, 94: 471–476; 1996). These differences were blurred with loss of statistical significance when the international diagnostic standard categories were applied. In manic patients, on the other hand, no amplitude differences compared to controls, and a topographical difference possibly indicating reduced frontal lobe control were found. The results revealed different neurophysiological mechanisms at the basis of the investigated subgroups and, thus, support the existence of different natural disease entities beyond the classical dichotomy of psychoses.

S70-5

MATERNAL GESTATIONAL INFECTIONS IN THE ETIOLOGY OF SCHIZOPHRENIC PSYCHOSES

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The contemporary neurodevelopmental hypothesis of schizophrenia and affective psychosis has emerged from pathobiological findings of early brain lesions and malformations of fetal brain development. In chronic schizophrenia we found that not the frequency, but the monthly distribution of maternal gestational infections was significantly different compared to controls. Twenty per cent of the mothers of schizophrenics recalled a manifest infection during pregnancy. The incidence of maternal gestational infections was significantly increased in the second trimester, especially during the fifth month of gestation. Respiratory infectious disesases (i.e. influenza and febrile cold) were frequent and accounted for 56% of all infections and of 64% of mid-pregnancy infections. Infections during mid-pregnancy were significantly associated with Leonhard's systematic schizophrenias with low familial aggregation of psychosis and a chronic non-remitting course with severe psychopathology. Furthermore, prenatal infections were significantly associated with the occurrence of further OCs, which are thought to constitute a significant risk factor for the development of schizophrenic psychosis. In our recent study, the cycloid psychoses with low heritability and good long-term prognosis were found to be significantly associated with first trimester respiratory infections (i.e. influenza, febrile cold). Acute respiratory infections explained 56% of all infections and all first trimester infections in cycloid psychosis. Furthermore, maternal infections seem to cause an early onset in cycloids. In manic-depression we failed to identify such associations to maternal gestational infections or other obstetric complications. These findings are suggestive that exogenously induced disturbances of fetal brain maturation during the first trimester of gestation are involved in the etiology of cycloid psychosis and those during the second trimester in systematic schizophrenias.

S71. Genetic epidemiology of mental illness

Chairs: P Munk-Jørgensen (DK), H Ewald (DK)

S71-1

ALZHEIMER'S DISEASE, GENETIC AND ENVIRONMENTAL FACTORS

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Several genetic and environmental factors have been implicated in Alzheimer's disease (AD). In recent years, considerable progress has been made in unraveling the genetic etiology. Three genes have been identified that are predominantly implicated in autosomal dominant forms of early-onset AD, the β-amyloid precursor protein gene and two homologous genes presenilin 1 and 2. Further, the apolipoprotein E gene (APOE) has been shown to be an important genetic risk factor for early- and late-onset AD. Although it is

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