ELEVATED PLASMA ENDOGENOUS NITRIC OXIDE SYNTHASE INHIBITOR MAY INDICATE ABNORMALITIES IN NMDA DEPENDENT NITRIC OXIDE PRODUCTION IN SCHIZOPHRENICS

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Nitric oxide synthesis can be inhibited by guanidino-substituted arginine analogues such as L-N^G-monomethylarginine (L-NMMA) and N^G,N^G-dimethylarginine (asymmetric dimethylarginine, ADMA) which is present in human plasma and urine. This raises the possibility that guanidino-substituted arginine analogues may exert a control mechanism on the brain nitric oxide synthase (NOS) and hence modulate nitric oxide (NO) metabolism which is also connected to NMDA subtype of glutamate receptor implicated in the pathophysiology of schizophrenia. Increased presence of an endogenous inhibitor of NOS in drug naive schizophrenic plasma samples was observed when schizophrenic plasma inhibited platelet NOS in vitro. We have investigated the plasma concentrations of ADMA and nitrate levels in drug naive schizophrenic patients and matched control subjects to see if endogenously produced NOS inhibitors is perturbed in schizophrenia.

Blood samples from 16 schizophrenic patients never exposed to neuroleptic treatment meeting DSM III-R criteria for schizophrenia were taken. Three of the above schizophrenic patients were treated with sulpiride 600 mg/day for 3 months. The main form of schizophrenia was paranoid but other types were also used. Nine healthy volunteers who had not taken any drugs for at least 2 weeks were used as controls. Plasma samples for ADMA were analyzed blindly by high-pressure liquid chromatography technique. Plasma ADMA levels in schizophrenic patients was elevated significantly compared to control subjects. Neuroleptic treatment in 3 patients seemed to have a lowering effect on ADMA levels. The cellular origins of methylarginines are not precisely known but the presence of free methyl and dimethylarginines in the brain were reported. Low CSF concentrations of cyclic guanosine 3'5'-monophosphate observed in schizophrenia may be related to the elevation of ADMA. The occurrence of these free methylarginines may have an important role in regulating the signal transduction through NMDA dependent NO metabolism in the brain, and suggest novel therapeutic targets.

FACTORS ASSOCIATED WITH SCHIZOPHRENIC RELAPSE: A RETROSPECTIVE STUDY

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The study was a retrospective investigation of the factors associated with relapse in one hundred consecutive schizophrenic patients who had suffered a clinical exacerbation and were admitted to San Carlos Hospital in Madrid. Reports of patients and significant others, and information from the medical records were used to determine whether patient had been compliant with treatment. A self-report scale predictive of drug compliance in schizophrenics was also used to assess subjective response to drug therapy.

We have recorded the following variables:
Illness variables
Marital status
Socioeconomic level
Level of family support
Therapeutic regimen prior to admission
Medication side effects
Patients' attitude toward health and illness
Incidence of stressfull life events
Alcohol and drug abuse comorbidity

This study offers preliminary evidence that sociodemographic factors and illness variables were unrelated to compliance, while treatment variables, especially side effects of medication, were associated with improved compliance. Noncompliant patients had significantly lack of feeling of illness and insight into it, and had more alcohol and drug abuse comorbidity. The compliant patients had higher incidence of adverse life events.

INFLUENCE OF GENDER AND FAMILY HISTORY ON THE AGE AT ONSET OF SCHIZOPHRENIA

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Family, twin and adoption studies have demonstrated that genetic factors play an important role in the pathogenesis and clinical expression of schizophrenia. Gender and family history have been suggested to influence the age at onset of the disease. In order to investigate this issue, 42 patients from 20 multi-affected families and 15 sporadic cases were personally examined. As age at onset was considered the age at the first appearance of clinical symptomatology, while the genetic loading for the familial cases was calculated on the basis of the number of affected and non-affected first-degree relatives.

For the familial cases, no difference was found between males and females concerning the age at onset (probands: males 21.5 yrs, females 22.1 yrs, $p > 0.1$; other family members: males 27.9 yrs, females 31.2 yrs, $p > 0.1$). Regarding the sporadic cases however, a difference was observed (males 20.6 yrs, females 25.2 yrs, $p < 0.05$). Additionally, among all the familial cases, the age at onset was found to be negatively correlated with the genetic loading only in females ($r = -0.37$, $p < 0.05$) and not in males ($r = -0.09$, $p > 0.1$).

These results support the hypothesis of the existence of two clinical subtypes of schizophrenia: one with common age at onset for both sexes and positive family history, and another with later age at onset for women and negative family history. The observation that, regarding the familial cases, the genetic loading influences the age at onset only in women, should be further evaluated in a larger sample of patients in relation to other clinical variables.

REDISCOVERING PROPFSCHIZOPHRENIE

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Emil Kraepelin first introduced the term 'Profpschizophrenie' in 1919. It was then defined as a sub-type of dementia praecox characterised by dull intellect, negative symptomatology and poor outcome. However, the negative symptomatology referred to by Kraepelin varied from that with which we are familiar with today.

Current research suggests that cognitive impairment is an integral component of schizophrenia. There is also evidence that the point prevalence of schizophrenia in individuals with mild learning disability is three times that seen in the normal population. Yet many studies of schizophrenia continue to exclude individuals with a premorbid history of mild learning disability. This study aims to redefine the psychopathology of schizophrenia as it occurs in patients with a premorbid I.Q. in the mildly learning disabled range (50–70).

57 subjects have been seen in three age and sex matched groups; subjects with a dual diagnosis of premorbid mild learning disability and schizophrenia (obtained from a National register, N = 21), sub-

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jects with DSMIII-R schizophrenia and normal premorbid I.Q. (randomly matched from the Lothian Psychiatric Case Register, N = 20), and subjects with mild learning disability alone (N = 16). The Quick I.Q. Test and The Positive and Negative Symptom Scale (PANSS) were administered to all 57 participants. A National Adult Reading Test (NART) was also performed on all schizophrenic control subjects to confirm a premorbid I.Q. within the normal range.

A one way ANOVA with Bonferroni Test for multiple comparisons was performed on symptom clusters (Positive, Negative and General), obtained from the PANSS. Dual diagnosis subjects showed significantly more negative symptoms (at p = 0.05) than either the schizophrenic group or the group of subjects with learning disability alone. Whereas the schizophrenic patients, without premorbid learning disability, showed significantly more positive symptoms than either the dual diagnosis or learning disability groups. Furthermore, regression analysis indicated a significant negative correlation between Quick I.Q. and negative symptomatology in all schizophrenic subjects.

This study confirms that preschizophrenic subjects with a low I.Q. develop a form of psychosis characterised by predominantly negative symptomatology.

THE LONG-TERM COURSE OF CHILDHOOD-ONSET SCHIZOPHRENIA. A SECOND FOLLOWUP OF 44 PATIENTS 27 YEARS AFTER THE FIRST FOLLOWUP AND 42 YEARS AFTER THE INITIAL PSYCHOTIC EPISODE: A FIRST REPORT

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First results of a long-term followup (M = 41.9 years, SD = 8.2 years) of 44 patients (19 males, 25 females) with Childhood-onset Schizophrenia are presented. Age at onset ranged from 7 to 14 years (M = 11.8 y., SD = 2.0 y.). Patients and/or their first-degree relatives were interviewed personally in 1994 with the Present-State-Examination (PSE) and the Disability-Assessment-Schedule (WHO-DAS) — about 27 years after the first followup. Clinical records were analyzed with the Instrument for the retrospective assessment of onset of Schizophrenia (WHO-IRAOS) and with sections of the PSE. The cases were re-diagnosed with DSM-III-R based on longitudinal data obtained between onset and first the first hospital admission. *Main results:* The cumulative prevalence of illness-onset with age is flatter in boys than in girls. An acute (vs. insidious) onset was significantly more frequent after 12 years of age. There was a negative correlation between age of onset and the social disability scores (WHO-DAS). 25% showed complete, 25% partial, and 50% very bad recovery at followup. None of the chronically psychotic patients showed an acute onset. The results are discussed with respect to epidemiology, gender differences, and etiological hypotheses of Childhood Schizophrenia.

DERMATOGLYPHICS OF SCHIZOPHRENIA

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Objectives: Dermatoglyphics elicit the genetic aetiology of many diseases. The genetically determined dermatoglyphic features include the total finger ridge count (TFRC), the A-B ridge and the ATD angle.

The pattern of the palmar flexion creases and the white lines were studied in addition to the genetic traits.

Methods: 80 schizophrenics (patients group) were compared to 100 psychiatrically free subjects (control group) using the inked method, results were compared with our findings in indiopathic epilepsy.

Summary of results: 1- Changes in the dermatoglyphic genetic traits were similar to those changes found in patients with idiopathic epilepsy.

2- Schizophrenics showed characteristic dermatoglyphic features of finger tips and palms which represent quantitative varying polygenic traits.

3- The pattern of the palmarflexion creases and the white lines showed different varieties that also indicate the polygenic nature of the disease.

Conclusions: 1- Schizophrenia is genetically determined and has a common aetiological relationship with idiopathic epilepsy.

2- The mode of genetic transmission in schizophrenia is polygenic.

SUSTAINED $5HT_{2A}$ RECEPTOR OCCUPANCY OF ZIPRASIDONE USING PET LIGAND ^{18}F SETOPERONE IN HEALTHY VOLUNTEERS

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Ziprasidone is a novel antipsychotic in late clinical development. The time course of its D_2 receptor occupancy has been previously demonstrated in healthy volunteers [1] and ziprasidone is associated with a low incidence of extrapyramidal side-effects (EPS). This study aimed to determine $5HT_{2A}$ receptor occupancy, and whether high occupancy may account for the low incidence of EPS. Eight healthy volunteers were each scanned on two separate occasions approximately 1 week apart. Nanomolar doses of ^{18}F-setoperone (7 mCi) were used as the $5HT_{2A}$ receptor ligand [2]. The first scan provided baseline binding for each individual. At pre-determined time points prior to the second scan, after at least 4 hours fasting, they received 40 mg ziprasidone orally, so that two volunteers were scanned at each time point post dose. Three-compartment modelling of setoperone pharmacokinetics was performed. The mean $5HT_{2A}$ receptor occupancy by ziprasidone is shown below:

	Ziprasidone receptor occupancy at various time points (hr)			
	4	8	12	18
5HT2A (%)	95.4	92.0	78.4	46.7
D2 (%)	79.4	68.2	52.8	32.2

Means of two individuals are shown, but differences between subjects were very small. Data on D_2 occupancy [1] obtained following the same dose of ziprasidone in a separate study are listed for comparison. Plasma levels of ziprasidone are being determined to confirm that exposure was similar in the two studies. *Conclusions:* $5HT_{2A}$ receptor occupancy in this study substantially exceeds the known D_2 occupancy at all time points. This may explain the low incidence of EPS with ziprasidone.

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THE ANATOMY OF THE FUNCTIONAL PSYCHOSES

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The idea that the 'functional' psychoses have their origins in brain as opposed to psychological dysfunction has a long history. Advances in imaging procedures have facilitated the study of brain architecture in psychiatric syndromes, and a number of correlates have emerged.

Using the Lothian Psychiatric Case Register, all patients discharged from in-patient care at the Royal Edinburgh Hospital during the years 1993 and 1994 with ICD-9 codes corresponding to the 'functional' psychoses (295, 296, 297 and 298) and aged between