British Journal of Psychiatry (1989), **155**, 536–544

Point of View

Age at Puberty and Mental Illness
Towards a Neurodevelopmental Aetiology of Kraepelin's Endogenous Psychoses*

LETTEN F. SAUGSTAD

The hypothesis of a neurodevelopmental aetiology of manic–depressive psychosis and schizophrenia is based on the relation between onset of puberty and the final regressive events in the central nervous system (elimination of 40% of neuronal synapses), and the discrepancy in body build in the two disorders which is similar to that between early- and late-maturing individuals. The marked rise in manic–depressive psychoses and decline in schizophrenia, particularly the non-paranoid categories, accompanying the decline in mean pubertal age by some four years during the past hundred years are taken as evidence that manic–depressive psychosis affects early maturers and schizophrenia particularly affects late maturers. Gender differences and social differentials accord with this theory. Redundancy of neuronal synapses characterises manic–depressive psychosis, and reduced density of synapses is a characteristic of schizophrenia, whereas 'normality', with optimal synaptic density, is in between.

The hypothesis is presented that the aetiology of manic–depressive psychosis (MDP) and schizophrenia is neurodevelopmental, arising from maturational irregularities in the central nervous system (CNS) in individuals with very early and extremely late puberty. This hypothesis is based on the relation between onset of puberty and the last major step in brain development, and the discrepancy in body build in MDP and schizophrenia which is similar to that between very early and extremely late maturing individuals.

In the human species, onset of puberty is considered to coincide with the final regressive event in the CNS (elimination of about 40% of neuronal synapses) (Huttenlocker, 1984; Ribchester, 1986; Goldman-Rakić, 1988: Rakić, 1989). Any irregularity at this stage will alter later brain function; such maturational irregularities are most likely to occur at the extremes of very early or extremely late puberty.

Early maturers (early puberty) tend to be pyknic (stocky), and late maturers tend to be leptosomic (slender) (Marshall & Tanner, 1986). According to Kretschmer (1921), pyknic body build predominated in MDP (90% of cases) and leptosomic in schizophrenia (80% of cases) at a time when only around 20% of the general population was of true pyknic or leptosomic build and mean age at menarche was around 15 years.

Age at puberty is only partly genetically determined. The decline in mean age at menarche from just below 17 years 100 years ago to around 13 years today in Western industrialised countries (Marshall & Tanner, 1986) is usually considered a phenotypic response to improved living conditions. Late maturers (mean + 2 s.d.) now experience menarche at about the same age (15 years) as early maturers (mean minus 2 s.d.) a century ago. Concomitantly, there has been a shift from a predominance of leptosomic–athletic and true leptosomic build to pyknic–athletic and true pyknic build. Following this decline in pubertal age, a significant rise in MDP is expected concomitant with a decline in schizophrenia, if MDP does indeed affect very early maturers and schizophrenia extremely late maturing individuals.

Trends in MDP

The Norwegian National Case Register of Serious Mental Disorder comprises all first admissions to psychiatric hospitals and clinics by diagnosis since 1916 (Ødegård, 1971; Saugstad & Ødegård, 1980, 1983, 1985). First admissions classified MDP or reactive depressive psychosis (ICD-9 category 298.0; World Health Organization, 1978) increased by more than 50% between 1926 and 1965. A majority of the latter is diagnosed MDP on readmission. In addition, an increasing proportion of hospital admissions was being classified as non-psychotic, particularly as depression (300.4), which has increased from less

* The hypothesis was first presented at the Annual Meeting of the Royal College of Psychiatrists, Brighton, 1–7 July 1988.

than 5% in the 1940s to above 10% in the '60s and now exceeds 20%. A great number of these patients are involuntarily admitted. Similarly in Denmark, where the Danish National Psychiatric Register covers admissions to psychiatric hospitals and clinics, the studies (Weeke *et al*, 1975; Nielsen & Bjørn-Henriksen, 1979) agree that MDP and depressive psychosis (298.0) occur with increasing frequency. In Iceland, Helgason (1979) in his follow-up study observed a lifetime risk of MDP of 3.34% as against 2.72% in 1947, and there was also a marked increase in depressive psychosis (298.0) and in non-psychotic depression (300.4). In the Lundby study from Sweden (Hagnell *et al*, 1982) of in-patients, out-patients, and untreated cases, the probability of suffering a depression increased significantly in both sexes over the period 1947–72, and the risk was highest among those aged 20–30 years. Similar observations have been made in the USA (Klerman, 1978), where there is an alarming increase of depression.

Trends in schizophrenia

Almost all cases of schizophrenia were admitted, and the admission rate probably approached 90% during 1921–40, and around 80% in the following 26 years in Norway (Ødegård, 1971; Saugstad & Ødegård, 1980, 1983; Saugstad, 1986). The narrowing of the concept of schizophrenia to a disorder with a necessarily poor prognosis, combined with a rising preference for diagnosing intermediate functional psychosis (ICD–9 297, 298, 299), and postponement of a diagnosis of schizophrenia until readmission complicate an assessment of its decline. However, taking into consideration Kretschmer's observation (1921) that the most severe subgroups of schizophrenics such as the non-paranoid (hebephrenia, catatonia, dementia simplex), were the most markedly leptosomic (dysplastic), suggesting that they represent extremely late maturers, a decline is probably mainly recorded in countries with a narrow concept of schizophrenia, such as Norway, Denmark, and Britain, among others.

In Norway, the lifetime risk of schizophrenia (including paranoid psychosis (297)) decreased in the male sex over 1926–65, and the decline is considerable in recent years, although it is not as marked as the reduction in schizophrenia diagnosed on first admission, which fell from more than 60% in 1926 to 19% in 1965, and to 5.5% in 1977–78 (both sexes together). In Denmark, there was a remarkable decline in first admissions for schizophrenia for both sexes over 1970–84 (Strømgren, 1987). We may question to what extent this reflects a true decline, since, of first admissions in 1972 who received the diagnosis that year or in the following 10 years, only 50% of the male and 40% of the female patients received the diagnosis on first admission (Munk-Jørgensen, 1985). A most remarkable feature was, however, the decreased proportion of resident schizophrenics, particularly women. In Scotland, first-admission rates dropped by as much as 40% between 1969 and 1978 (Eagles & Whalley, 1985), and in England and Wales (Saugstad & Ødegård, 1983) the proportion of schizophrenic first admissions (including paranoid psychosis) decreased slightly over 1970–77 (from 13.5% to 11.3%).

In contrast, the prevalence of schizophrenia is persistently high in poorer populations (e.g. in the Istrian region of Yugoslavia, in certain parts of rural Ireland, the Australian aborigines, the Cree Indians and the Salteaux of Northern Saskatchewan (Crocetti *et al*, 1964, 1971; Roy *et al*, 1971; Warner, 1985)). An excessive prevalence of schizophrenia (and extremely low prevalence of MDP) has repeatedly been observed in an isolated region of northern Sweden, where according to Bøøk (1953), as late as 1949, poverty was widespread and death rates were high. Moreover, Bøøk commented upon the uniformity of the clinical picture (a particular type of catatonia). Similar harsh conditions prevailed in the neighbouring regions of Finland, where the prevalence rates of schizophrenia are similarly elevated (Vaisanen, 1975; Lehtinen & Vaisanen, 1981).

Sex differences in age at onset and incidence of MDP

There is a markedly higher lifetime risk of MDP in women than men in most investigations (by 1.5–2.0 times) (Ødegård, 1972*a*; Strømgren, 1976; Rawnsley, 1982), in agreement with expectation from the hypothesis. Onset of MDP in women is also earlier than in men (maximum age-specific rates 30–40 years v. 40–50 years) (Lundquist, 1945).

Sex differences in age at onset and incidence of schizophrenia

It is usually believed that there is no sex difference in the incidence of schizophrenia, but a higher male incidence has been observed. In the USA, Babigan (1980) found higher male rates, and in Norway over 1926–65, Ødegård (1971) found 19% to 36% higher male admission rates. Higher male admission rates have also been recorded in Denmark (Strømgren, 1987), and in the Third World (Sartorius *et al*, 1986, 1987).

Onset of schizophrenia in men is, as expected, earlier than in women, with a difference in maximum age-specific rates of about ten years (Noreik & Ødegård, 1967; Ødegård, 1971). Earlier onset in men is distinguished by being more insidious, with greater chronic defects, and on the whole a less favourable course (Saugstad & Ødegård, 1980, 1986; Watt *et al*, 1983; Strømgren, 1987; Häfner, 1987).

With an earlier puberty (lower proportion of extremely late maturers) the female sex is 'protected' against schizophrenia with later, more acute onset, and a more favourable course. Being older at onset, there is relatively good preservation of the personality, which at that stage is already mature and fully developed, and female schizophrenics stay a shorter time in hospital, and spend longer out of hospital (Strømgren, 1987). This might explain the decrease of resident schizophrenics since 1953 in Denmark being much more pronounced for women. A more intensive study of the limited population of Bornholm in 1935 and in 1983 revealed a considerably decreased prevalence of female schizophrenics compared with a little-changed prevalence in men (Strømgren, 1987).

Trends in subgroups of schizophrenics

In Norway, over 1977–78, when 5.5% of the total 6255 first admissions were classified as schizophrenic, catatonia was diagnosed in only two women and four men, and dementia simplex and hebephrenia in 11 women and 21 men respectively. Whereas previously there had been a predominance of non-paranoid schizophrenia in the men, non-paranoid and paranoid schizophrenia were now about equally rare. In women paranoid schizophrenia predominated, whereas an equal proportion of non-paranoid and paranoid schizophrenics had been found in previous investigations (Saugstad & Ødegård, 1980).

This decline in the most severe subgroups such as the non-paranoid (hebephrenia, catatonia, dementia simplex) has often been accepted as due to drug treatment. The drugs cannot affect age at onset. The non-paranoid, with their most pronounced leptosomic (dysplastic) body build and particularly early and insidious onset, probably belong to the most extreme categories of late maturers. The marked reduction in these cases is therefore more likely a result of their significant reduction in the population. This is illustrated by the fact that Kretschmer's observation of leptosomic–dysplastic body build (acromegaloidism, eunuchoidism, infantilism, virilism in females, femininity in males, etc.) in 17.5% of schizophrenics (as against 0.4% in MDP) has received no attention lately. It might simply be due to a reduction in the numbers of these cases.

The relation between maturational rate and subgroup of schizophrenia is also illustrated from Asia and Africa, where ethnic groups are more mature throughout growth, with more weight for height than whites, and mature earlier (earlier age at puberty) (Marshall & Tanner, 1986). A greater predominance of paranoid over non-paranoid schizophrenia is observed, and onset is more acute and the course of the disease more favourable, with less chronic defects, than in the European countries included in the WHO study (Sartorius *et al*, 1986, 1987).

Trends in body build

Kretschmer's (1921) observations have been confirmed. There is a persistent discrepancy in body build in MDP and schizophrenia (Langfeldt, 1937). The association is now not so clear, because a rising proportion of cases of schizophrenia are unclassifiable (mixed type) (Astrup *et al*, 1962; Astrup & Noreik, 1966; Price, 1969; Singer, 1972). This has led to the opinion that Kretschmer himself overestimated the strength of the association. With considerably lower mean pubertal age and near disappearance of the extremes of body build in late maturers such as true leptosomic and considerable reduction in leptosomic–athletics, the association between body build and schizophrenia is apt to be less clear. The association has always been most pronounced in males, with puberty on average two years later than in females. The relation between body build and MDP is unaffected. Moreover, when MDP occurs in non-pyknic individuals, the course and prognosis are atypical (Mauz, 1930; Strømgren, 1976). The relation between body build and mental illness has also been confirmed in other ethnic groups (Verghese *et al*, 1978).

Concomitant with the decline in pubertal age, there is an increase in mean adult height of 13 cm and more weight for height. Weight for height has no Gaussian distribution, but the distribution is skewed toward the heavier weights, confirming a change in predominant body build toward the pyknic (stocky) type (Central Bureau of Statistics, 1988).

The social distribution of manic-depressives

Information relating social class to age at puberty is rarely available. A significantly higher rate of MDP in social class I than in the lower social classes has been observed in Finland (Stenbäck & Achté,

1966), in Iceland (Helgason, 1979), and in other countries (Rawnsley, 1982).

In Norway, the social differentials are negligible (Brundtland *et al*, 1980). Ødegård (1963, 1976*b*) followed all students leaving secondary schools in Norway between 1916 and 1929 until 1974, by means of the National Case Register: the female rate for MDP was 2.3 times higher than that in the general population, the male rate 1.7 times higher. The students represented only a few percent (<5%) of the relevant birth cohorts (1895–1910), in largely upper-middle-class families.

The social distribution of schizophrenics

An excess of schizophrenia in the lowest social classes (V) is one of the most consistent and debated findings in psychiatric epidemiology (Ødegård, 1972*b*, 1975*a*). The discrepancy concerns to what extent schizophrenics drift down to or were born and reared in social class V. In America, Hollingshead & Redlich (1958) maintained that the great majority were born and reared there, whereas in Britain Goldberg & Morrison (1963) found that the social distribution of the fathers of schizophrenics equalled that of the general population, and therefore that the schizophrenics drifted down either before or after onset of the disease. The studies are however not comparable, because the British social classification includes only occupation, whereas the Americans used weighted scores for place of residence, level of education, and occupation, which lowers the social class of previous generations. Further, the Americans included mainly chronic in-patients (10–15 years in hospital) adding to a probable social bias towards the lowest socio-economic class. In contrast, the British series could be biased towards the middle classes. This is because only 52% (351/672) of the series drawn by the Registrar General was considered. Among the 321 missing, 163 were excluded because "a large proportion of the patients whose entry could not be found had foreign names and were probably born abroad". The remaining 158 excluded (20–24 years old) were "difficult to interpret, they do not resemble the general population as closely as the fathers of patients aged 25–34 years" (Goldberg & Morrison, 1963). Most likely, therefore, an excess of schizophrenics are born and reared in the lowest socio-economic class, although not a majority (Saugstad, 1989*a*,*b*). The lack of excess of schizophrenics in the lowest class in the Hagerstown study (Clausen & Kohn, 1959) is not convincing. There were several confounding factors, such as the opening of a new private hospital in the middle of the study, with its effect on admission rates, selection of patients, and diagnoses. The number of cases was small, and there was no information on the proportion of single/married, male/female, distribution by occupation, or diagnostic criteria (Saugstad, 1989*a*).

The present minor social differentials in Norway, where no social classification has been constructed that differentiates significantly in mortality, led Ødegård (1975*a*) to use occupations. The total of 34 457 gainfully employed first admissions aged 20–69 years during 1926–50 were divided into 13 occupations. The highest admission rates for schizophrenia were observed in occupations with the lowest standard of training, income and social prestige. More particularly, in these occupations with a decreasing population (farm labourers, seamen) the rates increased in the last decade, whereas they declined in expanding occupations such as technicians.

Discussion

The rise in MDP, including depressive psychosis (ICD-9 298.0) and the decline in schizophrenia, particularly the non-paranoid categories (295.0, 295.1, 295.2), accompanying the significant decline in mean pubertal age in this century, have been taken as evidence suggesting that MDP affects very early maturers and schizophrenia late-maturing individuals, as have the sex differences in incidence and age at onset in MDP and schizophrenia. The different social distribution of MDP and schizophrenia, with an excess of MDP in the highest strata of society and of schizophrenia in the lowest, further strengthens the evidence for a neurodevelopmental aetiology involving maturational irregularities.

A frequent argument to account for the striking rise in depression has been increased social psychological strain. However, the mental disorders most associated with stress and life events are non-psychotic conditions such as the multiple depressive reactions (ICD-9 301.1, 308.1, 308.4, 311, 312, 313, 300.4). It is not usually possible to predict an outbreak of MDP, or relate it to a particular event. The "reactive or psychogenic" depressive psychoses (298.0) are by definition restricted to those which are "largely or entirely attributable to a recent life experience" (ICD-9). In practice, the diagnosis is frequently used without this requirement being fulfilled because of the reluctance to diagnose MDP or schizophrenia on first admission to hospital.

The growing reluctance to diagnose schizophrenia, the predominance of different concepts of the disease, changing diagnostic practice, as well as insufficient information, complicate an assessment of its decline (Saugstad & Ødegård, 1980, 1983,

1985). Furthermore, in countries with high unemployment, a number of schizophrenics are probably living in the community (Wiersma *et al*, 1983), receiving social benefits without ever having had a psychiatric examination. The striking decline in admissions classified as non-paranoid schizophrenia in Norway and Denmark is, however, accepted as reflecting a true decline, which is also illustrated from Denmark in the decrease in schizophrenic in-patients (Strømgren, 1987). There is no information from Britain concerning the decline in schizophrenia by subgroup.

Experienced psychiatrists like Ødegård (1972*a*) and Strømgren (1982) agree that the clinical picture of schizophrenia has changed continuously during the last 40–50 years, and that severe deterioration is now not often seen. We seem to observe an increasing number of acute, latent, schizoaffective and borderline psychotic conditions. These conditions have probably always been included in the concept of schizophrenia in the USA (until the introduction of DSM–III in 1980). They were possibly becoming increasingly frequent. This led Kasanin (1933) to introduce the concept of schizoaffective disorder, Hoch & Polatin (1949) latent or pseudoneurotic schizophrenia, Kety *et al* (1968) the spectrum schizophrenia, and Knight (1954) borderline schizophrenia. Subgroups of schizophrenics had already been described by French and German psychiatrists in the last century or the beginning of this century (Pichot, 1983). The unchanged, high proportion of first admissions classified schizophrenic in the USA in 1969 and 1975 (46.6%), without breakdown by subgroup, is therefore no argument against a decline in the most severe (least treatable) subgroups such as catatonia, hebephrenia and simple schizophrenia.

The non-paranoid schizophrenics with their extreme body build are probably those with the most delayed puberty, whereas puberty is possibly less delayed in paranoid schizophrenia and in subgroups with a favourable prognosis. In view of the relation between mean pubertal age and standard of living, we might speculate that the reason for the early introduction of the concept of intermediate functional psychoses (reactive or psychogenic) in Norway (1911) and Denmark (1916), for clinical conditions which in other countries would have been diagnosed as schizophrenia or MDP, was simply that these clinical pictures were comparatively more frequent because of the comparatively high standard of living (lower mean pubertal age).

Why is schizophrenia of early onset, particularly in the male sex?

A neurodevelopmental aetiology involving maturational irregularities in the CNS in extremely late-maturing schizophrenics implies that the attenuation of synaptic density goes beyond the optimal, and reduced synaptic density results. This reduction in density of synapses is invariably most pronounced in males, because of their later puberty. An earlier onset and more severe course is therefore to be expected.

The synapses that die are dispersed among those that survive, and we would therefore expect only subtle, unspecific structural cerebral deficits. Because regions of the neocortex, particularly the anterior and superior frontal cortex, are probably the last to reach adult levels of synaptic density (Rakič, 1989; Phelps *et al*, 1989), maximum reduction in density of synapses is expected in these regions. Verification of brain pathology specific to schizophrenia has not been easy. There is invariably considerable overlap between schizophrenics and controls. Several studies have had to rely on statistical comparisons of means in order to observe differences. However, there is agreement that the brain in schizophrenia is structurally abnormal. It manifests, in accordance with expectation, a condition of subtle structural deficits, often with a frontocortical maximum (Andreasen *et al*, 1982; Shelton & Weinberger, 1986). When cerebral atrophy is found, there is a high frequency of pre- and peri-natal morbidity (Shelton & Weinberger, 1986).

Clinically, it seems reasonable to consider the dependency of schizophrenics on their social environment (inability to choose their own suitable environment), because of their excessive vulnerability to overstimulation (high expressed emotions, noisome occupations, etc.) as well as to understimulation (social isolation), as reflecting their neurodevelopmental disorder. The detrimental effect of low IQ on the course and prognosis of the disease (Jones & Offord, 1975) is also in accord with the hypothesis if the neurodevelopmental disorder has this particular characteristic.

Why does MDP occur at any age, and particularly in females?

A certain shortening of the pre-pubertal growth period is probably accompanied by higher rates of elimination of synapses. In very early maturing MDP with a marked reduction in this final stage of brain reorganisation, irregularities and insufficient elimination of synapses could occur. It is suggested that incomplete final adjustment and a persistency of supernumerary synapses characterise MDP. The redundancy is most pronounced in the female sex with an earlier average puberty, and MDP is also more common. A redundancy of synapses is not

verifiable, even with our refined neuroradiological methods. The reports of "no definite pathological changes in the CNS" in the main group of MDP (Ashcroft, 1982) is therefore in agreement with expectation, as is the return of the personality to normal between the psychotic episodes. A psychotic breakdown can occur at any age, in the young (under 20 years) as well as in the old (over 70 years) (Stenstedt, 1952; Helgason, 1979), but the maximum age-specific rate is about 10 years earlier in women.

The insufficiency of genetics in MDP

The suggestion that MDP might be 'caused' by a single heterozygous genotype on chromosome 11 (Egeland *et al*, 1987), or in some cases by an allele on the X chromosome (Baron *et al*, 1987), is not contrary to the view that very early puberty is the necessary factor for the development of MDP. The allele by itself is not necessarily causative: less than 70% of those who inherit the allele develop the disorder.

The insufficiency of genetics in schizophrenia

Although a genetic aetiology for schizophrenia is highly convincing in studies of multiplex families, the low proportion of such multiply affected families and the great number of sporadic cases underline the uncertainty about a genetic component. The high discordance rate (>50%) in monozygotic twins stresses the insufficiency of a genetic factor. We (Saugstad & Ødegård, 1986*a*) were unable to demonstrate any significant correlation between inbreeding in rural communities in Norway in 1891 (mean 8.3%, range 4–31%) and first-admission rates to psychiatric hospitals over 1921–40 (>80% schizophrenic). Psychiatric morbidity as measured by first admission to psychiatric hospitals in Norway over 1926–55 (22 000 admissions) was also lower than expected among offspring of consanguineous parentage in comparison with the general population. In Helgason's (1979) investigation of all first-cousin marriages in Iceland during 1916–64, only the rates of mental retardation and organic syndromes were higher than in the controls.

Sherrington *et al* (1988) suggested a susceptibility locus for schizophrenia on chromosome 5. However, Kennedy *et al* (1988), in their investigation of the genetically homogeneous population of the isolated region in Northern Sweden (Bøøk, 1953), have produced strong evidence against such linkage. This is of particular interest since the population in question was traced back to three Finnish families settling in the region. The authors commented upon the predominance of severe subgroups of schizophrenia, in accordance with Bøøk's description from 1953. In this particular region where harsh conditions prevailed as late as 1949, mean pubertal age was probably well above the mean for Sweden, and the proportion of late-maturers considerably increased. Very late puberty as the necessary factor for the development of schizophrenia with its high prevalence in this area is clearly supported.

MDP and schizophrenia have existed as long as mankind

If MDP and schizophrenia are caused by maturational irregularities in the CNS of those maturing very early and extremely late respectively, then Kraepelin's endogenous psychoses have probably existed as long as mankind. Improvements in living conditions, which increase rate of maturation, increase the incidence of early maturers and thereby that of MDP, concomitantly with a decrease in late maturers and schizophrenia.

With this relation between standard of living, age at puberty, and the two mental disorders, the question arises as to whether standard of living in the last century in Europe was a recent achievement or of longer duration. That is to say, was the incidence of schizophrenia declining or stable? In Norway, with its late industrial revolution (latter half of the last century), a decline in living standard was prevented by massive overseas migration (second only to Ireland) (Saugstad, 1979). The living conditions in the above-mentioned northern Swedish area were probably not much different from those in Norway, and we would therefore imagine a similarly high prevalance of schizophrenia and an extremely low prevalence of MDP. This cannot be confirmed, despite the fact that Norwegian admission statistics go back to 1850. Attempts to conceptualise schizophrenia were first developed in the latter half of the century. Moreover, depressions were explicitly excluded from the census on insanity in 1835. In Norway as well as in England, the last century and the beginning of this were devoted to the immense social task of building mental hospitals. With inadequate hospital facilities, the most severe cases and new cases of schizophrenia were selected for admission. The last century was also a period of therapeutic optimism (moral treatment), an attitude which was essential in filling up the new hospitals, but which prevents any estimate of secular changes.

Anorexia nervosa – a disorder of early maturation?

The effect of gender and social class on maturational rate makes it reasonable to ask whether there are

https://doi.org/10.1192/bjp.155.4.536 Published online by Cambridge University Press

other disorders, more common in the female sex and upper-middle classes, and increasing in the population, in which early maturation could be involved. Anorexia nervosa and bulimia nervosa affect the female sex in particular and the upper-middle classes (Russel, 1983). They are steadily increasing, and they affect maturational rate. Moreover, there is clinical and experimental evidence of hypothalamic dysfunction in these disorders. There are also reports of the coexistence of MDP in some cases, and lithium has sometimes proved a successful treatment (Cantwell *et al*, 1977; Stein *et al*, 1982; De Vries, 1985).

No continuum of psychosis from MDP to schizophrenia

A continuum of psychosis from MDP to schizophrenia is unlikely if we accept a neurodevelopmental aetiology of Kraepelin's endogenous psychoses. This is because normality, with optimal density of synapses, is between the early-maturing MDP, with redundancy of synapses, and the late-maturing schizophrenia, with reduced synaptic density.

Schizophrenic disturbance of thinking is usually readily distinguished from manic–depressive mood swings. They are clearly different and specific psychopathological dimensions. However, the two disorders have also several symptoms in common, and we would expect similar areas and structures of the brain to be involved – those fundamental to emotional and cognitive behaviour (neocortex, limbic system, hypothalamus, etc.).

It seems reasonable to ask how it is possible to explain that a redundancy of synapses can result in excessive mood swings, whereas the attenuation of synaptic density is associated with cognitive defects. The hierarchical order of maturation in the CNS is probably crucial in this connection, because it implies that the sites of change differ in the two disorders. The phylogenetically oldest structures, such as the brainstem, thalamus, hypothalamus, etc., are the first to mature. The neocortex, particularly the anterior and superior part of the frontal cortex, is the last. So only in very early maturers could synaptogenesis be prevented in some of the phylogenetically oldest structures. In contrast we would expect maximum reduction in synaptic density to involve the anterior and superior part of the frontal cortex in late-maturing schizophrenics, such as has repeatedly been observed (Andreasen *et al*, 1982).

Schizophrenia – the final common path

Classic MDP, with its excessive mood swings and return of the normal personality between relapses, is unique: no single similar disease or injury has been identified. When MDP occurs in non-pyknic individuals, the course and prognosis are atypical (Mauz, 1930). In contrast, classic endogenous schizophrenia with its subtle non-specific structural deficits, although the most common, is but one of several schizophrenias. Several diseases (inherited and other) may present as schizophrenia. In these cases there are usually neurological signs and symptoms, and cerebral atrophy is often found (Propping, 1983; Saugstad & Ødegård, 1986*b*). Schizophrenia can also result from an early brain lesion affecting first and/or second regressive event in the CNS (at 4–5 months of pregnancy, or 1–2 years of life), which remains clinically unnoticed until around puberty when it interacts with the developmental regression of excessive interneuronal contacts (the final regressive event in the CNS) leading to the later onset of psychosis. Depending upon the site and extent of the primary lesion and rate of maturation, a variety of psychopathological conditions is observed in these cases, ranging from non-paranoid and paranoid, to the more favourable subgroups of schizophrenia, borderline conditions, and schizoaffective. Sometimes one has the impression of a continuum of psychosis, without, however, the inclusion of classic MDP. Finally, we observe cases of childhood psychoses (childhood schizophrenia, infantile autism) where the primary lesion prenatally and/or perinatally is in itself sufficient to affect early infant behaviour to such an extent. In such cases, onset of puberty is usually accompanied by an increase in EEG abnormalities, grand mal seizures, the mental defect often seems more severe, and a changing psychopathology is often observed which requires a change in medication. Because the early onset basically disturbs development, these psychoses are not directly comparable to adult schizophrenia. However, the characteristic perceptual disturbances, hypo- and hyper-responsiveness to stimuli as well as their fluctuating nature and the detrimental effect of low IQ, are comparable (Saugstad, 1989*a*).

Schizophrenia is therefore a final common path: a brain reaction to a variety of adverse factors acting pre-, peri- and post-natally. In contrast to MDP, personality does not return to normal between the psychotic episodes in schizophrenia. We observe personality change, and a longer stay in hospital is often needed, as well as chronic neuroleptic treatment. A reduction in these cases is therefore particularly desirable. Through our improvement in living conditions in this century, and in particular the reduction in the proportion of very late

maturers (late puberty) in the population, we have seen a reduction in the most severe, least treatable forms of the endogenous neurodevelopmental schizophrenia, the non-paranoid. Considering the exogenous schizophrenias, whether with onset in childhood or after puberty, but where a brain lesion pre- and/or perinatally is essential in the development of the disorder, we may ask whether a reduction in the sequelae of pre- and perinatal morbidity is in sight. Factors killing infants at or around birth are similar to those operating in pre- and/or perinatal morbidity (Saugstad, 1981). The significant reduction in infant mortality in this century is therefore probably also reflected in a reduction in the sequelae of pre- and perinatal morbidity. We may therefore already be experiencing a reduction in these schizophrenias with an exogenous aetiology. To gain more insight into these matters, and to enable comparison between different series of schizophrenics from different countries, we need to establish standardised criteria for optimal conditions, pre-, peri- and post-natally (Saugstad, 1981, 1985).

Acknowledgement

I am grateful to my friend and coworker, the late Ørnulv Ødegård, for sharing his great knowledge and clinical experience.

References

ANDREASEN, N. C., NASRALLAH, H. A., DUNN, V., *et al* (1982) Structural abnormalities in the frontal region in schizophrenia. *Archives of General Psychiatry*, **43**, 136–144.

ASHCROFT, G. (1982) Biochemistry and pathology of the affective psychoses. In *Handbook of Psychiatry 3: Psychoses of Uncertain Etiology* (eds J. K. Wing and L. Wing), pp. 160–165. Cambridge: Cambridge University Press.

ASTRUP, C., FOSSUM, A. & HOLMBOE, R. (1962) *Prognosis in Functional Psychoses*. Springfield Illinois: Thomas.

—— & NOREIK, K. (1966) *Functional Psychoses*. Springfield Illinois: Thomas.

BABIGAN, H. M. (1980) Schizophrenia. Epidemiology. In *Comprehensive Textbook of Psychiatry, III* (eds H. I. Kaplan, A. M. Freedman and B. J. Sadock), pp. 1121–1131. Baltimore: Williams & Wilkins.

BARON, M. N., RISCH, R., HAMBURGER, B., *et al* (1987) Genetic linkage between X-chromosome markers and bipolar affective illness. *Nature*, **326**, 289–292.

BOOK, J. A. (1953) A genetic and neuropsychiatric investigation of a North Swedish population. *Acta Genetica (Basel)*, **4**, 1–100.

BRUNDTLAND, G. H., LIESTØL, K. & WALLØE, L. (1980) Height, weight and menarcheal age of Oslo school children during the last 60 years. *Annals of Human Biology*, **7**, 307–322.

CANTWELL, D. P., STURZENBERG, S., BUTTOUGHS, J., *et al* (1977) Anorexia nervosa, an affective disorder. *Archives of General Psychiatry*, **34**, 1087–1093.

CENTRAL BUREAU OF STATISTICS (1988) *Yearbook 1988*. Oslo: Central Bureau of Statistics.

CLAUSEN, J. A. & KOHN, M. L. (1959) Schizophrenia and the social structure. In *Epidemiology of Mental Disorder*, Publication 60 (ed. B. Pasamanick), pp. 69–94. Washington, DC: American Association for the Advancement of Science.

CROCETTI, G. M., KULCAR, Z., KESIC, B., *et al* (1964) Differential rates of schizophrenia in Croatia, Yugoslavia. *American Journal of Public Health*, **54**, 196–206.

——, LEMKAU, P. V., KULCAR, Z., *et al* (1971) Selected aspects of the epidemiology of psychoses in Croatia, Yugoslavia. *American Journal of Epidemiology*, **94**, 126–134.

DE VRIES, M. (1985) Anorexia nervosa and affective disorder. *American Journal of Psychiatry*, **142**, 1–2.

EAGLES, J. K. & WHALLEY, L. J. (1985) Decline in the diagnosis of schizophrenia among first admissions to Scottish mental hospitals from 1969–78. *British Journal of Psychiatry*, **146**, 151–54.

EGELAND, J. A., GERHARDT, D. S., PAULS, D. L., *et al* (1987) Bipolar affective disorder linked to DNA markers on chromosome 11. *Nature*, **325**, 783–787.

GOLDBERG, E. M. & MORRISON, S. L. (1963) Schizophrenia and social class. *British Journal of Psychiatry*, **109**, 785–802.

GOLDMAN-RAKIĆ, P. S. (1989) Development of cortical circuity. *International Wallenberg Symposium on Neurobiology of Early Infant Behaviour. Stockholm: 28 August–1 September 1988*. New York: Plenum.

HÄFNER, H. (1987) The epidemiology of schizophrenia. In *Search for the Causes of Schizophrenia* (eds H. Häfner, W. F. Gattaz and W. Yanzarik), pp. 47–74. Stuttgart: Springer Verlag.

HAGNELL, O., LANKE, J., ROHRSMAN, B., *et al* (1982) Are we entering an age of melancholy? *Psychological Medicine*, **12**, 279–289.

HELGASON, T. (1979) Epidemiological investigations concerning affective disorders. In *Origin, Prevention and Treatment of Affective Disorder* (eds M. Schou & E. Strømgren), pp. 241–255. London: Academic Press.

HOCH, P. H. & POLATIN, P. (1949) Pseudoneurotic forms of schizophrenia. *Psychiatric Quarterly*, **23**, 248–276.

HOLLINGSHEAD, A. B. & REDLICH, F. C. (1958) *Social Class and Mental Illness*. New York: John Wiley & Sons.

HUTTENLOCKER, P. R. (1984) Synapses: elimination and plasticity in developing human cerebral cortex. *American Journal of Mental Deficiency*, **88**, 488–496.

JONES, M. B. & OFFORD, D. R. (1975) Independent transmission of IQ and schizophrenia. *British Journal of Psychiatry*, **126**, 185–190.

KASANIN, J. (1933) The acute schizo-affective psychosis. *American Journal of Psychiatry*, **13**, 97–126.

KENNEDY, J. L., GLUFFRA, L. A., MOISES, H. W. *et al* (1988) Evidence against linkage of schizophrenia to markers on chromosome 5 in a northern Swedish pedigree. *Nature*, **336**, 167–170.

KETY, S. S., ROSENTHAL, D., WENDER, R., *et al* (1968) The types and prevalence of mental illness in the biological and adoptive families of adopted schizophrenics. In *The Transmission of Schizophrenia* (eds D. Rosenthal & S. S. Kety). New York: Pergamon Press.

KLERMAN, G. L. (1978) Affective disorders. In *Harvard Guide to Modern Psychiatry* (eds M. Armand & M. D. Nicholi Jr), pp. 253–281. Cambridge, Mass: Belknap Press.

KNIGHT, R. P. (1954) Borderline states. In *Psychoanalytic Psychiatry and Psychology* (eds R. P. Knight & C. R. Freidman). New York: Internal University Press.

KRETSCHMER, E. (1921) *Körperbau und Charakter*. Heidelberg: Springer Verlag.

LANGFELDT, G. (1937) *The Prognosis in Schizophrenia and the Factors influencing the Course of the Disease*. Copenhagen: Munksgård.

LEHTINEN, V. & VAISANEN, E. (1981) Epidemiology of psychiatric disorder in Finland. *Social Psychiatry*, **16**, 61–180.

LUNDQUIST, G. (1945) Prognosis and course in manic-depressive psychoses. *Acta Psychiatrica Scandinavica* (suppl. 35).

MARSHALL, W. A. & TANNER, J. M. (1986) Puberty. In *Human Growth*, vol. II (eds F. Falkner & J. M. Tanner, pp. 171–209. New York: Plenum Press.

MAUZ, F. (1930) *Die Prognostik der Endogenen Psychosen*. Stuttgart: Thieme Verlag.

MUNK-JØRGENSEN, P. (1985) Decreasing first admission rates of schizophrenia among males in Denmark from 1970 to 1984. *Acta Psychiatrica Scandinavica*, **73**, 645–650.

NIELSEN, A. & BJØRN-HENRIKSEN, I (1979) Prevalence and disease expectancy for depressive psychoses. In *Origin, Prevention and Treatment of Affective Disorders* (eds M. Schou & E. Strømgren), pp. 199–206. London: Academic Press.

NOREIK, K. & ØDEGÅRD, Ø. (1967) Age at onset of schizophrenia in relation to socio-economic factors. *British Journal of Psychiatry*, **124**, 243–249.

ØDEGÅRD, Ø. (1963) Mental disease in Norwegians with a high-school background. *Acta Psychiatrica Scandinavica*, **39**, 31–40.

—— (1971) Hospitalized psychoses in Norway. Time-trends in 1926–65. *International Journal of Social Psychiatry*, **6**, 53–58.

—— (1972*a*) The multifactorial theory of the inheritance in predisposition to schizophrenia. In *Genetic Factors in Schizophrenia* (ed. A. R. Kaplan), pp. 256–295. Springfield, Illinois: Thomas.

—— (1972*b*) The epidemiology of the psychoses. In *Psychiatrie der Gegenwart*, band II, teil 1 (eds K. P. Kisker, J.-E. Meyer, M. Müller & E. Strømgren), pp. 213–258. Heidelberg: Springer Verlag.

—— (1975*a*) Social and ecological factors in the etiology, outcome, treatment and prevention of mental disorders. In *Psychiatrie der Gegenwart*, band III (eds K. P. Kisker, J.-E. Meyer & E. Strømgren), pp. 151–198. Heidelberg: Springer Verlag.

—— (1975*b*) Morbidity and social mobility in an upper class educational group. *Acta Psychiatrica Scandinavica*, **52**, 36–48.

PHELPS, M., CHUGANI, H. T. & MAZZIOTTA, J. C. (1989) Metabolic assessment of functional maturation and neuronal plasticity of the human brain. In *International Wallenberg Symposium on Neurobiology of Early Infant Behaviour. Stockholm: August 28–September 1, 1988*. New York: Plenum Press.

PICHOT, P. J. (1983) *A Century of Psychiatry*. Paris: Roger Dacosta.

PRICE, J. (1969) An anthropometic comparison of psychiatric patients and their siblings. *British Journal of Psychiatry*, **115**, 435–442.

PROPPING, P. (1983) Genetic disorders presenting as "schizophrenia". *Human Genetics*, **65**, 1–10.

RAKIĆ, P. (1989) Development of the primate visual pathway. *International Wallenburg Symposium on Neurobiology of Early Infant Behaviour, Stockholm August 28–September 1, 1988*. New York: Plenum Press.

RAWNSLEY, K. (1982) Epidemiology of affective psychoses. In *Handbook of Psychiatry 3, Psychoses of Uncertain Etiology* (eds J. K. Wing & L. Wing), pp. 134–140. Cambridge: Cambridge University Press.

RIBCHESTER, R. R. (1986) *Molecule, Nerve and Embryo*. Glasgow: Blackwell.

ROY, C., CHOUDHURE, A. & IRVINE, D. (1971) The prevalence of mental disorders among Saskatchewan Indians. *Journal of Cross-Cultural Psychology*, **1**, 383–392.

RUSSEL, G. F. M. (1983) Anorexia nervosa and bulimia nervosa. In *Handbook of Psychiatry 4: The Neuroses and Personality Disorders* (eds G. F. M. Russel & L. A. Hersov), pp. 285–297. Cambridge: Cambridge University Press.

SARTORIUS, N., JABLENSKY, A., KORTEN, A., *et al* (1986) Early manifestations and first-contact incidence of schizophrenia in different cultures. *Psychological Medicine*, **16**, 909–928.

——, ——, ERNBERG, G., *et al* (1987) Course of schizophrenia in different countries. Some results of a WHO international comparative 5-year follow-up study. In *Search for the Causes of Schizophrenia* (eds H. Häfner, W. F. Gattaz & W. Janzarik), pp. 107–113. Berlin: Springer Verlag.

SAUGSTAD, L. F. (1979) Crude death and infant mortality 1840–1900 in Norway, Sweden, Denmark and England & Wales. *Scandinavian Population Studies*, **5**, 83–97.

—— (1981) Weight of all births and infant mortality. *Journal of Epidemiology and Community Health*, **35**, 185–191.

—— (1985) The relation between nature and nurture in mental subnormality. *Nordisk Psykiatrisk Tidsskrift*, **39**, 85–94.

—— (1986) An example from the Norwegian register. In *Psychiatric Case Registers in Public Health* (eds G. T. ten Horn, R. Giel, W. Gulbinat & J. H. Henderson), pp. 44–60. Amsterdam: Elsevier.

—— (1989*a*) Social class, marriage and fertility in schizophrenia. *Schizophrenia Bulletin*, **15**, 9–43.

—— (1989*b*) Mental illness and cognition in relation to age at puberty. *Clinical Genetics*, **35**, 1–12.

—— & ØDEGÅRD, Ø. (1980) Ingen internasjonal tilnaerming. *Nordisk Psykiatrisk Tidsskrift*, **34**, 455–464.

—— & —— (1983) Persistent discrepancy in international diagnostic practice since 1970. *Acta Psychiatrica Scandinavica*, **68**, 501–510.

—— & —— (1985) In defence of international classification. *Psychological Medicine*, **15**, 1–2.

—— & —— (1986*a*) Inbreeding and schizophrenia. *Clinical Genetics*, **39**, 261–271.

—— & —— (1986*b*) Huntington's chorea in Norway. *Psychological Medicine*, **16**, 39–48.

—— & —— (1987) Inbreeding and the epidemiology of schizophrenia. In *Human Genetics* (eds F. Vogel & K. Sperling), pp. 466–473. Berlin: Springer Verlag.

SHELTON, K. & WEINBERGER, D. R. (1986) X-ray computerized tomography studies in schizophrenia. In *Handbook of Schizophrenia* vol. I. (eds H. A. Nasrallah & D. R. Weinberger), pp. 207–250. Amsterdam: Elsevier.

SHERRINGTON, R., BRYNJOLFSSON, J., PETURSSON, H. *et al* (1988) Localization of a susceptibility locus for schizophrenia on chromosome 5. *Nature*, **336**, 164–167.

SINGER, K. (1972) Physique, personality and mental illness in the southern Chinese. *British Journal of Psychiatry*, **121**, 315–319.

STEIN, G. S., HARTSHORN, J., JONES, J., *et al* (1982) Lithium in a case of severe anorexia nervosa. *British Journal of Psychiatry*, **140**, 526–528.

STENBÄCK, A. & ACHTÉ, K. A. (1966) Hospital first-admissions and social class. *Acta Psychiatrica Scandinavica*, **42**, 113–125.

STENSTEDT, A. (1952) A study in manic-depressive psychosis. *Acta Psychiatrica et Neurologica Scandinavica* (suppl. 79).

STRØMGREN, E. (1976) *Psykiatri* (12th edn). Copenhagen: Munksgård.

—— (1982) Development of concepts of schizophrenia, subclassification of schizophrenia. In *Handbook of Psychiatry 3, Psychoses of Uncertain Etiology* (eds J. K. Wing & L. Wing), pp. 3–7, 13–16, 28–32. Cambridge: Cambridge University Press.

—— (1987) Changes in the incidence of schizophrenia? *British Journal of Psychiatry*, **150**, 1–7.

VAISANEN, E. (1975) Psychiatric disorders in Finland. *Acta Psychiatrica Scandinavica* (suppl. 263), 22–33.

VERGHESE, A., LARGE, P. & CHIU, E. (1978) Relationship between body build and mental illness. *British Journal of Psychiatry*, **132**, 12–15.

WARNER, R. (1985) Recovery from schizophrenia. *Psychiatry and Political Economy*, p. 380. London: Routledge & Kegan Paul.

WATT, D. C., KATZ, K. & SHEPHERD, M. (1983) The natural history of schizophrenia. *Psychological Medicine*, **13**, 663–670.

WEEKE, A., BILLE, M., VIDEBECH, T., *et al* (1975) Incidence of depressive symptoms in a Danish county. *Acta Psychiatrica Scandinavica*, **51**, 28–41.

WIERSMA, R., GIEL, R., DE JONG, A., *et al* (1983) Social class and schizophrenia in a Dutch cohort. *Psychological Medicine*, **13**, 141–150.

WORLD HEALTH ORGANIZATION (1978) *Mental Disorders. Glossary and Guide to Their Classification in Accordance with the Ninth Revision of the International Classification of Disease* (ICD-9). Geneva: WHO.

Letten F. Saugstad, MD, PhD, *The National Case Register, Behrensgt 5-0257, Oslo 2, Norway*