Schizophrenia Research, 10 (1993) 7–14

SCHRES 00295

Puberty and the onset of psychosis

Paloma M. Galdos[a], Jim J. van Os[b] and Robin M. Murray[c]

[a]*Department of Child and Adolescent Psychiatry, The Bethlem Royal and Maudsley Hospitals, London, UK,* [b]*Genetics Section, Department of Psychological Medicine, Institute of Psychiatry, London, UK and* [c]*Department of Psychological Medicine, King's College Hospital and Institute of Psychiatry, London, UK*

(Received 3 September 1992; revision received 2 November 1992; accepted 9 November 1992)

According to the neurodevelopmental hypothesis of schizophrenia, maturational events in the brain at puberty interact with congenital defects to produce psychotic symptoms. As girls reach puberty at a younger age than boys, we predicted that (i) females would show earlier onset of psychotic illness arising around puberty, and (ii) onset of psychosis in females would be related to menarche. Analysis of epidemiological data regarding admission to psychiatric units in (a) England over the period 1973–1986, (b) France over the period 1975–1980, as well as examination of 97 psychotic adolescents referred to an adolescent unit over a 14 year period, supported both these propositions.

Key words: Puberty; Menarche; Age of onset; Gender difference; Schizophrenia

INTRODUCTION

'Then what a change in the mental activity of the brain does the period of puberty cause. Looking at the matter from the combined point of view of physiologists and psychologists, we must connect the new development of the affective faculties, the new ideas, the new interests in life, the new desires and organic cravings, the new delight in certain sort of poetry and romance, with a new evolution of function in certain parts of the brain that had lain dormant before' (Thomas Clouston, 1892).

Why do the characteristic delusions and hallucinations of schizophrenia seldom occur before adolescence? Several recent explanations have been proposed along the lines originally put forward by Clouston in his discussion of 'developmental insanity'. According to these, late developmental events in the brain underlie the emergence of psychotic symptoms (Feinberg, 1982/83; Weinberger, 1987; Murray et al., 1988; Saugstad, 1989). Because early adolescence is a period of profound endocrine changes, many have speculated that the process of puberty triggers the maturational events that produce psychosis; indeed, Kraepelin (1909) already considered that menarche and onset of psychosis were related.

Puberty occurs in the growing boy or girl as the gonads change from the infantile to the adult state, but there are marked sex differences in the timing of its principal manifestations. The adolescent growth spurt begins in girls at about the age of 10.5, and in boys at about 12.5 years of age (Marshall and Tanner, 1986). There are smaller differences in the age at which the first secondary sex characteristics appear; boys' genitalia begin to develop four months to 1 year later than girls' breasts (Taranger & Karlberg, 1976; Taranger et al., 1976; Largo and Prader, 1983a,b). The steepest rise in testosterone concentrations in boys occurs between about 12 and 14 years of age; in girls the most dramatic rise of estradiol is between 11 and 13 years of age (Preece, 1986).

If puberty underlies the events that initiate schizophrenia, as some neurodevelopmental theories predict, then, since puberty in females declares

Correspondence to: J.J. van Os, Department of Genetics, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK.

itself at a younger age than in males, onset of psychosis around puberty should follow this trend. To examine the hypothesis that the differential onset of puberty in males and females results in earlier onset of psychotic symptoms in girls, we examined data regarding first admissions to mental illness hospitals in both England and France. In order to examine diagnostic issues and to establish the relationship between menarche and onset of psychosis, we also studied a sample of adolescents, referred to a regional adolescent unit in South London.

EPIDEMIOLOGICAL STUDIES

England

Figures were obtained from the Department of Health regarding first admissions for schizophrenia and paranoia (ICD 295, 297) to psychiatric hospitals and units in England over the period 1973–1986. As shown in Fig. 1, the first admission rates show a dramatic increase from the age of 15 years in both sexes; this increase is more accentuated in males. To further examine sex differences, we calculated male to female ratios of first admission rates in consecutive age groups, as shown in Fig. 2. Between ages 10 and 14 years, the rate ratio is 0.85, indicating a slight, non-significant, female excess ($z = 0.50$, $p = 0.3$, 95% C.I. 0.62–1.17). This is followed by a sharp increase in the male to female ratio in each quinquennium until the age of 25 years, and a more gradual decline afterwards. To examine whether the rate ratio shows real variation between age strata, we tested the hypothesis that the ratios in different strata were the same

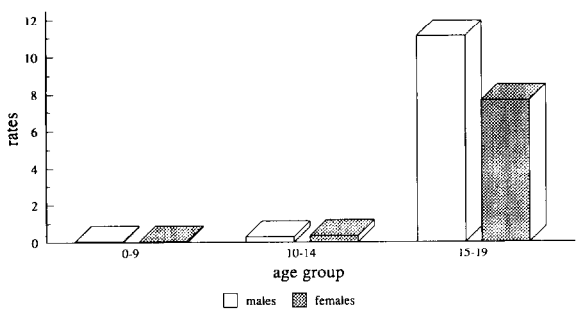

Fig. 1. First admission rates of schizophrenia and paranoia per 100.000 population by age group. England 1973–1986.

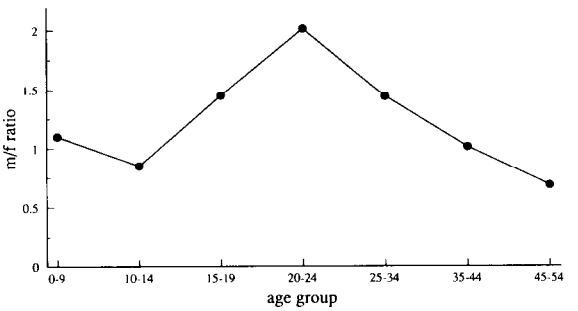

Fig. 2. Male to female ratios of first admission rates per 100.000 population for schizophrenia and paranoia by age group. England 1973–1986.

as their pooled summary estimate. The Mantel Haenszel test of the heterogeneity of the rate ratio (Rothman, 1986) across the strata 10–14 years and 15–19 years, revealed that the observed difference of ratios was highly significant ($\chi^2 = 10.39$, $p < 0.01$).

France

Several authors have shown that different diagnostic criteria for schizophrenia produce differences in the ratio of male to female patients (Lewine, 1984; Castle et al., 1991). The above epidemiological findings might therefore be due to the particular diagnostic habits of U.K. psychiatrists, and might not exist in a country where different diagnostic criteria are applied. Therefore, we also examined epidemiological data from France. In this country, a distinction is made between 'schizophrénies chroniques' on the one hand, and 'bouffée délirante' on the other (INSERM, 1969). Schizophrenia is regarded as a chronic syndrome, with onset mostly before the age of 30 (Pichot, 1982, 1984); similarities between the French concept and schizophrenia as defined in DSM-III have been noted (Kellam, 1989). Bouffée délirante refers to acute short-lived psychosis, and may correspond to either acute schizophrenia, affective or other psychosis in ICD-9 (Johnson-Sabine et al., 1983).

Figures were obtained from the Institut National de la Santé et de la Recherche Médicale in Paris concerning first admissions for schizophrenia (INSERM code 02) to state mental illness hospitals and units in France over the period 1975–1980. As shown in Fig. 3, the trend in male to female ratios across age strata is virtually identical to that in England.

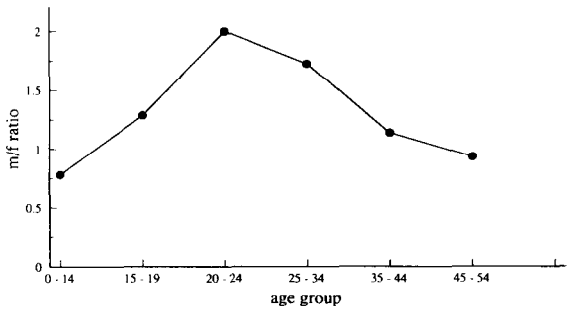

Fig. 3. Male to female ratios of first admission rates per 100.000 population for schizophrenia by age group. France 1975–1980.

CLINICAL STUDY

Subjects referred between 1976 and 1990 to the regional adolescent unit at the Bethlem Royal Hospital in South London were selected for study. Nearly all had been in-patients in the unit, which has a flexible male to female bed ratio. Parental and family interviews form a routine part of the multidisciplinary assessment. All medical, nursing, social work, and occupational therapy notes of subjects whose discharge summary indicated the presence of any psychotic symptom (i.e. delusion, hallucination, thought disorder or at least two of the following: catatonia, incongruity of affect, blunted affect) were scrutinized by PG. All correspondence and accessory information was also examined. The quality of note-taking in the Bethlem Royal Hospital is high, with considerable standardization of history taking (Institute of Psychiatry Training Committee, 1973). Psychotic symptoms were defined as indicated by Wing et al. (1974), and were rated on a three point scale where 0 indicated that the symptom was absent, 1 that it was doubtfully present or was minimal in severity, and 2 that it was definitely present. Based on all available information, an estimate was made of the age of onset of the disorder. Onset was defined as the emergence of psychotic symptoms that were described with sufficient clarity to rate as 2. Similarly, the age of first contact with psychiatric services for psychosis was also determined. Age of menarche for girls, defined as onset of menstruation, as recorded in the notes was ascertained.

Sample characteristics

103 subjects (age range 12–18) with psychotic symptoms were identified. Of these, 6 were excluded because of gross organic pathology. The final sample thus consisted of 49 males and 48 females. 53% of the sample were Caucasian, 35% Afro-Caribbean, and 12% of other ethnic origin.

The ICD discharge diagnoses of the 97 subjects are shown in Table 1. There were no significant differences between males and females as regards ethnicity, presence of mental retardation, or ICD diagnosis, although more females had a diagnosis of affective psychosis. Only two subjects, a boy and a girl, were described in the medical notes as prepubertal.

Age of onset

The mean age of onset of psychotic symptoms was significantly higher for males (mean = 14.8, S.D. = 1.3) than for females (mean = 14.1, S.D. = 1.1, $p = 0.006$). Age of first contact with services for psychotic symptoms was also significantly higher for males ($p = 0.016$). Breakdown by diagnostic category shows that this is largely due to a sex difference in age of onset which was present in the schizophrenic group, but not in the non-schizophrenic group (Table 2). These findings were independent of definition of age of onset (table 2). To facilitate comparison with our epidemiological samples, we divided subjects with a diagnosis of schizophrenia or schizo-affective disorder into two groups, one with onset before the age of 15 and one age 15 or older, for each of the two definitions of onset. We then compared the numbers of males and females in each group in a 2×2 design, using the chi-square statistic with continuity correction

TABLE 1

ICD-9 diagnosis by sex in 97 psychotic adolescents

	Males	*Females*
Schizophrenia	26	24
Schizo-affective disorder	7	8
Bipolar disorder	1	4
Depressive psychosis	0	2
Other psychosis	15	10
Total	49	48

TABLE 2

Mean age of onset by sex and diagnostic category

	*Schizophrenia**		*Non-schizophrenic psychoses*	
	Males (S.D.)	*Females (S.D.)*	*Males (S.D.)*	*Females (S.D.)*
Age of onset of psychosis	14.9 (1.3)	14.0** (1.1)	14.5 (1.4)	14.3 (1.1)
Age of first contact with services	15.1 (1.3)	14.3** (1.1)	14.6 (1.3)	14.4 (1.0)

*Including schizo-affective disorder.
**$p < 0.01$.

to test for significance. There were significantly more girls in the early onset group (Table 3).

These findings might be biased in that boys, because of later onset of puberty, could remain longer than girls under the care of child psychiatric services rather than those for adolescents. We therefore examined records of admissions to the Maudsley children department with a psychotic discharge diagnosis (ICD 295, 296, 297, 298 and 299) over a five year period, and found only two boys and one girl aged 11 or older, who had presented with non-organic psychosis as defined in our inclusion criteria. None had been referred to the adolescent unit in the first instance. All three were under the age of 13, and reanalysis of our data, taking into account these admissions to the child psychiatric department (based on the assumption that over fourteen years there would have been 6 male and 3 female admissions with psychosis), showed no significant difference from the original results. It is therefore unlikely that our sample was biased in this sense.

TABLE 3

Onset of psychotic symptoms by sex and age group in the group of schizophrenic subjects*

Age of onset psychosis	*Males*	*Females*	χ^2 *(p)*
11–14	9	23	11.2
15–18	24	9	(<0.001)
Age first contact psychosis			9.8 (<0.01)

*Including schizo-affective disorder.

Menarche

In those girls in whom both the age of menarche and age of onset of psychotic symptoms was recorded in the notes (schizophrenia $n = 20$, other diagnoses $n = 12$), the mean delay between menarche and onset of psychotic symptoms was 1 year, 4 months. There were no significant differences in mean delay between the different diagnostic groups. In 59%, onset was within one year after menarche and in 88% within two years. There was a significant correlation between age at menarche and onset of first psychotic symptom ($r = 0.54$; $p = 0.001$) (Fig. 4).

DISCUSSION

The findings

Examination of first admission rates of individuals who received a diagnosis of schizophrenia or paranoia in England over a 13 year period demonstrated a slight, non-significant female excess in

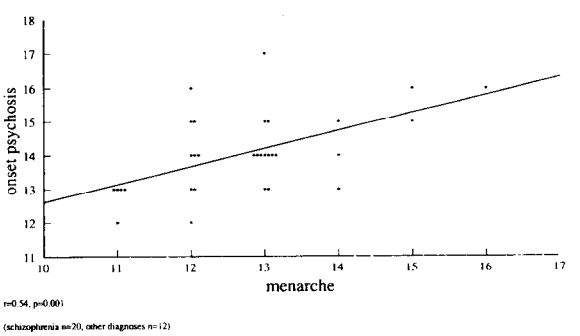

Fig. 4. Onset of psychosis and menarche: scatterplot and linear regression.

the age group 10–14 years, followed by a growing male surplus as rates rose sharply with increasing age. There was a highly significant change in the male to female ratio across the age strate 10–14 years and 15–19 years. These findings were replicated in France. Furthermore, we found that the majority of females in our clinical sample had onset of psychosis within one year after menarche, and that the two were significantly related.

It appears, therefore, that there is no male excess in schizophrenia around puberty, and although our evidence is not definitive, it is suggestive of earlier onset in girls. This conclusion, however, is seemingly at odds with the well replicated finding that males manifest schizophrenia at an earlier age than females (Lewine et al., 1981; Loranger, 1984; Angermeyer and Kühn, 1988). Comparison of age distribution curves for schizophrenia consistently show a higher proportion of young males and an excess of older females (Castle and Murray, 1991). Sex distribution curves, however, are not isomorphic and some girls do manifest schizophrenia in adolescence. Because of the small numbers of very early onset cases in most studies, trends regarding sex differences around the time of puberty are likely to be obscured, and to date no study has addressed this issue specifically.

From the child psychiatric literature, however, it can be inferred that very early onset cases do not necessarily follow the adult pattern. Although many authors have described an excess of boys among schizophrenics with onset in earlier childhood (e.g. Green et al., 1984; Russel et al., 1989), there appears to be a trend towards an increasing proportion of female patients near puberty. For instance, in the study of Green et al. (1984) the male to female ratio in subjects with DSM-III schizophrenia was 7 : 1 for the age range 6–8 years but fell to 1 : 1 at 9–11 years. Reanalysis of data from Gillberg (Gillberg, 1986; personal communication, 1992), regarding a population-based survey of all teenagers (age range 13–19) treated as inpatients for operationally defined psychotic disorders, demonstrates that for schizophrenia there was a significantly earlier age of onset in girls. Bettes and Walker (1987) showed that in a sample of 1084 children aged 5–18 years with a psychotic diagnosis (nearly 90% schizophrenia), there was a dramatic increase in positive symptoms such as delusions and hallucinations in girls between ages 9–10 and 11–12 years, whereas boys showed this increase between ages 11–12 and 13–14 years. These findings corroborate our results.

Our epidemiological data allowed us only to analyze for sex differences in 5 year age groups, and we were not able to produce age distribution curves for both sexes based on data over single years. The change in the sex ratio over quinquennia, however, has been used in many previous studies to demonstrate differential age of onset for males and females in schizophrenia (e.g. Lewine et al., 1981; Loranger, 1984). Our clinical sample was not epidemiologically based, but it is difficult to conceive how bias could operate in, for instance, very young female schizophrenics being admitted to hospital, but not their male counterparts.

It would appear that the dramatic rise in psychotic symptomatology around puberty takes place earlier in females than in males, followed by a substantial male preponderance later in adolescence.

Interpretation

The temporal association between puberty and onset of psychosis begs the question of what the exact nature of this relationship might be. Little is known about the relation between puberty and various developmental processes that may precipitate psychosis. Some authors (Feinberg 1982/83; Saugstad, 1989), citing evidence that the developmental regression of excessive interneuronal contacts persists into the second decade of life (Huttenlocher, 1979), have suggested that schizophrenia may arise as the result of errors in this process of maturational reorganization of the human brain. The reduction in synaptic density, however, starts well before puberty, and it is therefore unlikely that this process is triggered by, for instance, sex hormones (Feinberg, 1990). Others (Weinberger, 1987; Murray et al., 1988) advanced the theory that this process of synaptic pruning, or other developmental changes during pubescence, may allow latent, congenital defects in neurodevelopment to become manifest. Animal studies have provided a model of how a fixed congenital lesion could remain relatively unapparent until the age of sexual maturation, and then have a profound impact on behaviour (Goldman and Alexander, 1977). Apart from synaptic pruning, a number of other late developmental events

could provide a 'permissive' environment for the latent defect to be uncovered during the adolescent period. For instance, myelination in the corticolimbic circuitry during late adolescence may serve to trigger psychotic illness (Benes, 1989), and sex hormones possibly affect myelination (Timiras, 1972).

The course of the development of the brain's dopamine systems led Finch and Morgan (1987) to speculate that asynchrony in dopamine receptor ageing might cause schizophrenia. The finding of Wong et al. (1984), that dopamine receptors in the striatum and frontal cerebral cortex showed a different pattern of decline in males and females may also be relevant in this regard. The role of sex hormone secretion in adolescence has been considered by many authors. For instance, estrogen may have a direct effect on synaptic structure (Olmos et al., 1987). Hruska and Silbergeld (1980) reported an enhancement of striatal dopamine response by the female sex hormone; a sudden surge of gonadal steroids could set off a chain of chemical events in predisposed individuals, resulting in illness. However, a potent anti-dopaminergic activity of estrogens has also been described (Raymond et al., 1978), and female sex hormones may thus act as a protective factor in schizophrenia by raising the vulnerability threshold for psychosis in women (Seeman, 1985; Häfner et al., 1991). If estrogen acts as a biological modulator, its protective effect might not be established until late adolescence, as secretion of the gonadotrophins and principal gonadal steroids in its regular cyclical pattern will not be established immediately after menarche; only 14% of menstrual cycles are ovulatory in the first year postmenarche, with 50% ovulatory by 3 years (Apter, 1980). This would mean that before completion of the changes associated with puberty, girls are susceptible to psychosis, and that afterwards they are protected for some time, whereas in boys puberty does not have such a protective effect. Our finding of an excess of girls in early adolescence, followed by a male surplus after the age of 15 is, therefore, compatible with such an estrogen protection effect.

Another interpretation to consider is that psychological and biological changes associated with puberty may cause a subgroup of girls, who are genetically predisposed, to develop a psychotic illness. For instance, stress or hormonal changes associated with menarche may act as a precipitant. Fluctuation of hormone levels has been implicated in the development of puerperal psychosis (Kumar and Brockington, 1988), and several surveys have demonstrated an increase in the number of admissions for psychotic disorders during the paramenstrual phases of the menstrual cycle (4–5 days before and during the onset of menses) (e.g. Targum et al., 1991).

More research is needed in order to clarify the temporal relationship between puberty and the onset of psychosis. Much could be learned from study of morbid risk of psychosis in relatives of subjects with very early onset psychosis. A number of non-invasive techniques have been used to assess brain maturational processes, such as magnetic resonance imaging (Jernigan et al., 1990), electroencephalography (Feinberg, 1982/83) and evoked potentials (Lafrenière et al., 1990). Exploration of the functional significance of these maturational processes in relation to the onset of psychosis could provide a challenging arena for the study of brain-behaviour relationships.

ACKNOWLEDGEMENTS

We thank Mr F. Oliphant of the Department of Health in London, and Prof. M. Bourgeois of the University of Bordeaux for providing the epidemiological data, Dr S. Wessely for statistical advice, and Dr D. Steinberg for making possible the case-note study.

REFERENCES

Angermeyer, M. and Kühn, L. (1988) Gender differences in age at onset of schizophrenia. Eur. Arch. Psychiatr. Neurol. Sci. 237, 351–364.

Apter, D. (1980) Serum steroids and pituitary hormones in female puberty: a partly longitudinal study. Clin. Endocrinol. 12, 107–120.

Benes, F.M. (1989) Myelination of cortical-hippoccampal relays during late adolescence. Schizophr. Bull. 15, 585–593.

Bettes, B.A. and Walker, E. (1987) Positive and negative symptoms in psychotic and other psychiatrically disturbed children. J. Child Psychol. Psychiat. 28, 555–568.

Castle, D.J., and Murray, R.M. (1991) The neurodevelopmental

basis of sex differences in schizophrenia. Psychol. Med. 21, 565–575.

Castle, D.J., Wessely, S., Der, G. and Murray, R.M. (1991) Is operationally defined schizophrenia more common in men? Paper presented at the International Congress on Schizophrenia, Tn: April 21–25.

Clouston, T. (1892) In Clinical Lectures on Mental Diseases, 3rd edn. London: Churchill.

Feinberg, I., Thode, H.C. Jr, Chugani, H.T. and March, J.D. (1990) Gamma distribution model describes maturational curves for delta wave amplitude, cortical metabolic rate and synaptic density. J. Theoret. Biol. 142, 149–61.

Feinberg, I. (1982/83) Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? J. Psychiatr. Res. 17, 319–34.

Finch, C.E. and Morgan, D. (1987) Aging and schizophrenia: a hypothesis relating asynchrony in neural aging processes to the manifestations of schizophrenia and other neurological diseases. In: Schizophrenia and Aging (Eds. N.E. Miller and D. Cohen) pp. 97–108. New York: Guilford.

Gillberg, C. (1986) Teenage psychoses: epidemiology, classification and reduced optimality in the pre-, peri- and neonatal periods. J. Child Psychol. Psychiatry 27, 87–98.

Goldman, P.S. and Alexander, G.E. (1977) Maturation of prefrontal cortex revealed by local reversible cryogenic depression. Nature 267, 613–615.

Green, W.H., Campbell, M., Hardesty, A.S., Grega, D., Padron-Gayol, M., Shell, J. and Erlenmeyer-Kimling, L. (1984) A comparison of schizophrenic and autistic children. J. Am. Acad. Child Psychiatry 23, 399–409.

Hruska, R.E. and Silbergeld, E.K. (1980) Increased dopamine receptor sensitivity after estrogen treatment using the rat rotation model. Science 208, 1466–1468.

Huttenlocher, P.R. (1979) Synaptic density in human frontal cortex-development changes and effects of aging. Brain Res. 163, 195–205.

Institut National de la Santé et de la Recherche Médicale, Section Psychiatrie (1969) Classification Française des Troubles Mentaux. Bull. Inst. Natl. Santé Rech. Méd. 24, (suppl. 2).

Institute of Psychiatry Training Committee. (1973) Notes on Eliciting and Recording Clinical Information. Oxford: Oxford UP.

Jernigan, T.L. and Tallal, P. (1990) Late changes in brain morphology observable with M.R.I. Dev. Med. Child Neurol., 32, 379–85.

Johnson-Sabine, E.C., Mann, A.H., Jacoby, R.J., Wood, K., Peron-Magnan, P., Olie, J. and Deniker, P. (1983) Bouffée délirante: an examination of its current status. Psychol. Med. 13, 771–778.

Kellam, A.P.M. (1989) French empirical criteria for the diagnosis of non-affective non-organic psychoses. Comparison between the criteria suggested by Professors Pull and Pichot and those of DSM-IIIR. Br. J. Psychiatry 155, 153–159.

Kraepelin, E. (1909) In Psychiatrie, ein Lehrbuch für Studierende und Ärtzte. Leipzig: Barth.

Kumar, R. and Brockington, I.F. (1988) In Motherhood and Mental Illness: Causes and Consequences. Bristol: Wright.

Lafrenière, L., Laureau, E., Vanasse, M., Forest, L. and Ptito, M. (1990) Maturation of short latency evoked potentials by median nerve stimulation: a cross-sectional study in a large control group of children. In: New Trends and Advanced Techniques in Clinical Neurophysiology (EEG Suppl. 41) (Eds. P. Rossini and F. Mauguière) pp. 236–242. Amsterdam: Elsevier.

Largo, R.H. and Prader, A. (1983a) Pubertal development in Swiss boys. Helv. Paediatr. Act., 38, 211–228.

Largo, R.H. and Prader, A. (1983b) Pubertal development in Swiss girls. Helv. Paediatr. Act., 38, 229–243.

Lewine, R., Straus, J. and Gift, E. (1981) Sex differences in age at first hospital admission for schizophrenia: fact or artefact. Am. J. Psychiatry 138, 440–444.

Lewine, R., Burbach, D. and Meltzer, H. (1984) Effect of diagnostic criteria on the ratio of male to female schizophrenic patients. Am. J. Psychiatry 141, 84–87.

Loranger, A.W. (1984) Sex difference in age at onset of schizophrenia. Arch. Gen. Psychiatry 41, 157–161.

Marshall, W.A. and Tanner, J.M. (1986) Puberty. In Human Growth vol. II (Eds. F. Falkner and J.M. Tanner) pp. 171–209. New York: Plenum Press.

Murray, R.M., Lewis, S.W., Owen, M.J. and Foerster, A. (1988) The neurodevelopmental origens of dementia praecox. In Schizophrenia: the Major Issues (Eds. P. Bebbington and P. McGuffin) pp. 90–107. Oxford, Heinemann.

Olmos, G., Aquilera, P., Tranque, P., Naftolin, F. and Garcia-Segura, L. (1987) Estrogen induced synaptic remodelling in adult rat brain is accompanied by the reorganization of neuronal membranes. Brain Res., 425, 57–64.

Pichot, P. (1982) The diagnosis and classification of mental disorders in French speaking countries: background, current view and comparison with other nomenclature. Psychol. Med., 12, 475–492.

Pichot, P. (1984) The French approach to classification. Br. J. Psychiatr., 144, 113–118.

Preece, M.A. (1986) Prepubertal and pubertal endocrinology. In Human Growth vol. II (Eds. F. Falkner and J.M. Tanner) pp. 211–224. New York: Plenum.

Raymond, V., Beaulieu, M., Labrie, F. and Boissier, J.R. (1978) Potent antidopaminergic activity of estradiol at the pituitary level of prolactin release. Science 200, 1173–1175.

Rothman, K.J. (1986) Modern Epidemiology. Boston: Little, Brown and Company.

Russel, A.T., Bott, L. and Sammons, C. (1989) The phenomenology of schizophrenia occurring in childhood. J. Am. Acad. Child and Adol. Psychiatry 28, 399–407.

Saugstad, L.F. (1989) Social class, marriage, and fertility in schizophrenia. Schiz. Bull. 15, 9–43.

Seeman, M.V. (1985) Sex and schizophrenia. Can. J. Psychiatr., 30, 313–315.

Taranger, J. and Karlberg, P. (1976) The somatic development of children in a Swedish urban community: VII. Graphic analysis of biological maturation by means of maturograms. Act. Paediatr. Scandinav. (Suppl.) 258, 136–146.

Taranger, J., Lichtenstein, H. and Svennberg-Redegren, I. (1976) The somatic development of children in a Swedish urban community. VI. Somatic pubertal development, Act. Paediatr. Scandinav. (suppl.) 258, 121–135.

Targum, S.D., Caputo, K.P. and Ball, S.K. (1991) Menstrual cycle phase and psychiatric admissions. J. Affect. Dis., 22, 49–53.

Timiras, P. (1972) Physiologic changes at adolescence. In Developmental Physiology and Aging (Ed. P.S. Timiras) pp. 364–374. New York: Macmillan.

Weinberger, D.R. (1987) Implications of normal brain development for the pathogenesis of schizophrenia. Arch. Gen. Psychiatry 44, 660–669.

Wing, J.K., Cooper, J.E. and Sartorius, N. (1974) The Measurement and Classification of Psychiatric Symptoms. London: Cambridge UP.

Wong, D.F., Wagner, H.N., Dannals, R.F., Frost, J., Ravert, H., Wilson, A., Rosenbaum, A., Gjedde, A., Douglass, K., Petronis, J., Folstein, M., Toung, T., Burns, D. and Kuhar, M. (1984) Effects of age on dopamine and serotonin receptors measured by positron tomography in the living human brain. Science 226, 1393–1396.

Yakovlev, P.I. and Lecours, A.R. (1964) The myelogenetic cycles of regional maturation of the brain. In Regional Development of the Brain in Early Life (Ed. A. Minkowski) pp. 3–70. Boston: Blackwell.