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SPECIAL ISSUE

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Epidemiology of schizophrenia: the global burden of disease and disability

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Abstract Evidence from nearly a century of epidemiological research indicates that schizophrenia occurs in all populations with a prevalence in the range of 1.4 to 4.6 per 1000 and incidence rates in the range of 0.16–0.42 per 1000 population. Multi-centre studies conducted by the World Health Organization have highlighted important differences between 'Western' and 'Third World' populations as regards the course and outcome of the disorder, with a significantly better prognosis in the developing countries. The factors underlying the better outcome of schizophrenia in developing countries remain essentially unknown but are likely to involve interactions between genetic variation and specific aspects of the environment. These features place schizophrenia, along with diabetes, cancer and hypertension, into the group of genetically complex diseases which are characterised by polygenic transmission, locus heterogeneity and environmental contribution to causation. The emerging pattern of risk factors and antecedents of schizophrenia suggests multiple, mainly quantitative deviations from the average developmental trajectory, primarily in the areas of early neurodevelopment, cognitive ability and social behaviour. These deviations are compatible with the notion of non-specific background factors facilitating the operation of genetically determined causal pathways. Research likely to result in new insights should focus on the population distribution and behavioural effects of potential risk factors and markers suggested by biological and genetic research

Key words Schizophrenia · Dementia praecox · Incidence · Prevalence · Lifetime risk · Outcome · Crosscultural comparisons

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Introduction

For over a century, epidemiological research into schizophrenia (Jablensky 1999) has been revolving around four essential questions: (i) what is the "true" population frequency of the disorder and how is it distributed across and within various population groups? (ii) do the incidence, manifestations and course of schizophrenia vary in relation to factors of the physical and social environment? (iii) who is at risk and what determines the risk? (iv) can the answers to these questions help explain what causes the disorder and how to prevent it?

The earliest application of an epidemiological method to the investigation of psychoses was the work of a woman physician, Jenny Koller, who examined the aggregation of psychiatric disorders in the families of 284 probands and 370 healthy subjects in the canton of Zürich using a prototype case-control design (Koller 1895). Anticipating much later findings of genetic epidemiology, she reported that "the hereditary loading of the healthy subjects is much higher than generally assumed"; that "the strongest loading is that of psychoses and accentuated characters"; and that "the loading in distant relatives is quite low, unless a person at risk is exposed to multiple factors".

Kraepelin (1904) saw clearly the potential of population research to "throw light on the causes of mental disorder" and advocated comparative studies of the psychoses and personality traits across different cultures. In the first half of the 20th century, epidemiological research into the psychoses took two distinct directions. Whereas the focus of European investigators was primarily on issues of heredity, North American researchers developed a strong interest in the social ecology of mental illness (Faris and Dunham 1939). However, epidemiological research was pursued vigorously on both sides of the Atlantic and the contours of the epidemiological map of schizophrenia were by and large complete before World War II. Most of the methodological tools of psychiatric epidemiology were developed and applied with considerable success during the four decades between 1910 and 1950.

Developments in methodology

To a greater extent than studies of other complex diseases, the epidemiological investigation of schizophrenia encounters serious methodological problems at the level of case finding and ascertainment. First, the criteria defining schizophrenia depend critically on the ability to elicit and interpret self-reports of subjective experience; the prerequisite clinical skills cannot be easily translated into simple tools for case finding in the field. Secondly, no biological test or psychometric trait marker of the liability to schizophrenia is yet available for use in population screening. Thirdly, schizophrenia is a low-incidence and low-prevalence disorder and population-based case finding through door-to-door interviewing is costly.

In the 1980s great hopes for epidemiology were pinned on the development of explicit diagnostic criteria, incorporated in the DSM-III (APA 1980) and its successors, and, a few years later, the ICD-10 (WHO 1992). Two types of assessment instruments were developed and linked to the new diagnostic criteria. The NIMH Diagnostic Interview Schedule, DIS (Robins et al. 1981) and the related WHO-ADAMHA Composite International Diagnostic Interview, CIDI (Robins et al. 1988) are fully structured interviews targeting the DSM-IIIR and ICD-10 criteria. They are sometimes referred to as "verbatim" interviews, because the interviewer is required to read out to the respondent each word in the interview without deviations from the script. The interviewer makes no judgements about the presence or absence of psychopathology; rather, the interviewer records the judgements of the respondent. Lay interviewers with no clinical skills can be trained to administer the DIS or the CIDI in about a week. The advantage of these interview protocols is that they are inexpensive and have been shown to be reliable [for example, the test-retest kappa for the CIDI diagnosis of schizophrenia is 0.70 (Wittchen et al. 1991)]. However, their validity for the identification of psychotic symptoms is problematic. Reliance on self-report leads inevitably to emphasis on symptoms at the expense of signs; but for schizophrenia, signs like flat affect, odd behaviour, speech disorder and apathy may be critical for a correct diagnosis. Using clinicians as reference, the sensitivity of the DIS diagnosis of schizophrenia was found to be only 24% (Anthony et al. 1985). Therefore, the capacity of the new "verbatim" instruments for valid detection of psychotic disorders in community respondents is limited.

Semi-structured clinical interviews such as the 10th edition of the Present State Examination (PSE), now incorporated in the Schedules for Clinical Assessment in Neuropsychiatry, SCAN (Wing et al. 1990), cover a broad range of psychopathology and require clinical skills to elicit data that can be processed by ICD-10 and DSM-IV diagnostic algorithms. The SCAN and similar interviews are suitable as second-stage diagnostic instruments but there is a clear need for a relatively simple and psychometrically sound screening procedure for case finding of schizophrenia in field surveys, as the available candidates for first-stage screen (DIS and CIDI) have not been successful.

Contributions of epidemiology to the description of the schizophrenic syndrome

Prevalence

An overview of selected prevalence studies of schizophrenia is presented in Table 1. The studies differ in many aspects of methodology but have in common a high intensity of case finding. Several studies are repeat surveys in which the original population has been reinvestigated following an interval of 10 or more years (the resulting consecutive prevalence figures are indicated by →).

The majority have produced prevalence estimates in the range 1.4 to 4.6 per 1000 population at risk. However, these are crude prevalence figures which may not be directly comparable due to demographic differences such as age-specific mortality and migration. Therefore, the modal prevalence of 1.4 to 4.6 per 1000 may not reflect the true extent of variation among different populations. Certain populations and groups deviate from the central tendency. Unusually high rates (2–3 times the national or regional rate) have been reported for isolate populations in northern Sweden (Böök et al. 1978), several areas in Finland (Lehtinen 1996); and for an area in Croatia with high out-migration during the 19th and early 20th century (Crocetti et al. 1971). At the other extreme, a virtual absence of schizophrenia and a relatively high rate of depression has been claimed for the Hutterites in South Dakota, a Protestant sect whose members live in closely-knit endogamous communities sheltered from the outside world (Eaton & Weil 1955). Negative selection for schizoid individuals who fail to adjust to the communal lifestyle and eventually migrate without leaving progeny has been proposed but not definitively proven as an explanation.

Low prevalence rates have also been reported for some Pacific island populations (Torrey et al. 1974) but uncertainties about case finding makes the interpretation of such reports problematic. Two carefully planned surveys in Taiwan (Rin & Lin 1962; Lin et al. 1989) were separated by 15 years during which major social change had taken place. While the total mental morbidity increased, the prevalence of schizophrenia decreased from 2.1 to 1.4 per 1000. In both surveys, the indigenous Taiwanese had significantly lower rates than the mainland Chinese who had migrated to the island after World War II.

The results of the Epidemiologic Catchment Area (ECA) study in the United States (Robins & Regier 1991) which indicate a higher prevalence rate than most other studies, are difficult to interpret. Inconsistencies among the study areas (such as a 13-fold difference in the rates for age group 18–24 across the sites) suggest that the diagnostic procedure, involving the DIS administered by lay interviewers, may have resulted in a number of false positive diagnoses. In the more recent National Comorbidity Survey (NCS), diagnoses of 'non-affective psychosis' by computer

Table 1 Selected prevalence studies of schizophrenia

Author	Country	Population	Method	Prevalence per 1000 population
Surveys in developed countries				
Brugger (1931)	Germany	Area in Thuringia (n=37 561); age 10+	Census	2.4
Strömgren (1938); Bøjholm and Strömgren (1989)	Denmark	Island population (n=50 000)	Repeat census	3.9 → 3.3
Lemkau et al. (1943)	USA	Household sample	Census	2.9
Essen-Möller et al. (1956); Hagnell (1966)	Sweden	Community in southern Sweden	Repeat census	6.7 → 4.5
Crocetti et al. (1971)	Croatia	Sample of 9201 households	Census	5.9
Rotstein (1977)	Russia	Population sample (n=35 590)	Census	3.8
Robins & Regier (1991)	USA	Aggregated data across 5 ECA sites	Sample survey	7.0 (point) 15.0 (lifetime)
Jeffreys et al. (1997)	UK	London health district (n=112 127)	Census; interviews of a sample (n=172)	5.1
Jablensky et al. (2000)	Australia	4 urban areas (n=1 084 978)	Census; interviews of a sample (n=980)	3.1–5.9 (point)[a] 3.9–6.9 (one year)[b]
Surveys in developing countries				
Rin and Lin (1962); Lin et al. (1989)	Taiwan	Population sample	Repeat census	2.1 → 1.4
Bash and Bash-Liechti (1969)	Iran	Rural area (n=11 585)	Census	2.1
Dube and Kumar (1972)	India	Four areas in Agra (n=29 468)	Census	2.6
Padmavathi et al. (1987)	India	Urban (n=101 229)	Census	2.5 (point)
Salan (1992)	Indonesia	Slum area in West Jakarta (n=100 107)	Two-stage survey: (a) key informants; (b) interview	1.4 (point)
Lee et al. (1990)	Korea	Urban and rural	Census	Lifetime: 3.0 (urban) 4.0 (rural)
Chen et al. (1993)	Hong Kong	Community sample (n=7229)	DIS interviews	Lifetime: 1.2 (males) 1.3 (females)
Waldo (1999)	Kosrae (Micronesia)	Island population (n=5500)	Key informants & clinic records; some interviews	6.8 (point), age 15+
Kebede et al. (1999)	Ethiopia	District (n=227 135) south of Addis Ababa; mixed urban & rural	Two-stage survey: (a) door-to-door & key informants; (b) SCAN interviews	7.1 (point), age 15–49

[a] All psychoses; [b] schizophrenia and other non-affective psychoses

algorithm based on a version of the CIDI were found to agree poorly with clinicians' diagnoses based on telephone re-interviews, resulting in discrepant estimates of the lifetime prevalence of both 'narrowly' and 'broadly' defined psychotic illness (Kendler et al. 1996).

The question whether major differences exist in the prevalence of schizophrenia in different populations has no simple answer. The majority of studies have found similar prevalence rates though a small number of populations clearly deviate from the central tendency. However, the magnitude of such deviations in schizophrenia is small compared to 10-fold to 30-fold differences in the prevalence of other multifactorial diseases (e. g. ischaemic heart disease, diabetes, multiple sclerosis) that have been observed across populations.

Incidence

The incidence rate is a better estimate of the 'force of morbidity' (the probability of disease occurrence at a point in time) in a given population. Its estimation depends on how reliably the point of onset can be determined. Since it is not possible at present to determine the time of onset of any cerebral dysfunction or biochemical lesion underlying schizophrenia, the onset of the disorder is usually defined

as the point in time when its clinical manifestations become apparent. The first hospitalisation is not a good index of the 'true' onset, due to the variable time lag between the earliest appearance of symptoms and the first admission. A better approximation is provided by the first contact with any psychiatric or general medical service which is accessed by symptomatic individuals for the first time.

Table 2 presents the findings of 13 incidence studies of schizophrenia. Studies using a 'broad' definition of schizophrenia (ICD-8 or ICD-9) suggest that rates based on first admissions or first contacts vary about threefold, between 0.17 and 0.54 per 1000 population per year. Studies using restrictive criteria such as the Research Diagnostic Criteria (Spitzer & Endicott 1978), DSM-III and its successors, or ICD-10 report incidence rates that are two to three times lower than those based on 'broad' criteria.

Up to date, the only study which has generated directly comparable incidence data for different populations is the WHO ten-country investigation (Sartorius et al. 1986; Jablensky et al. 1992). Incidence rates in the WHO study were estimated from first-in-lifetime contacts with any 'helping agency' (including traditional healers in the developing countries) which were monitored prospectively over a two-year period. Potential cases and key informants were interviewed by clinicians using standardised instruments, and the timing of onset was ascertained for the majority of the patients. In 86% of the 1022 patients the first manifestation of diagnostic symptoms of schizophrenia was within a year of the first contact and, therefore, the first-contact rate was accepted as a reasonable proxy for the onset of psychosis. Two definitions of 'caseness' were used: a 'broad' clinical classification comprising ICD-9 schizophrenia and paranoid psychoses and a restrictive definition including 'nuclear' schizophrenia with Schneiderian first-rank symptoms (Wing et al. 1974). The rates for 12 catchment areas are shown in Table 3.

The differences between rates for 'broad' schizophrenia (0.16–0.42 per 1000) across the study areas were significant ($p < 0.001$, two-tailed test); however, those for 'nuclear' schizophrenia were not. Since the cases of 'nuclear'

Table 2 Selected incidence studies of schizophrenia

Author	Country	Population	Method	Rate per 1000
A. Europe and North America				
Ødegaard (1946)	Norway	Total population	First admissions 1926–1935 (n=14 231)	0.24
Häfner and Reimann (1970)	Germany	City of Mannheim (n=330 000)	Case register	0.54
Lieberman (1974)	Russia	Moscow district (n=248 000)	Follow-back of prevalent cases	0.20 (male) 0.19 (female)
Helgason (1964)	Iceland	Total population	First admissions 1966–1967 (n=2388)	0.27
Castle et al. (1991)	UK	London (Camberwell)	Case register	0.25 (ICD) 0.17 (RDC) 0.08 (DSM-III)
Nicole et al. (1992)	Canada	Area in Quebec (n=338 300)	First admissions	0.31 (ICD) 0.09 (DSM-III)
McNaught et al. (1997)	UK	London health district (n=112 127)	Two censuses, 5 years apart	0.21 (DSM-IIIR)
Brewin et al. (1997)	UK	Nottingham	Two cohorts of first contacts (1978–1980 and 1992–1994)	0.25 → 0.29 (all psychoses) 0.14 → 0.09 (ICD-10 schizophrenia)
B. Asia and the Caribbean				
Raman and Murphy (1972)	Mauritius	Total population (n=257 000)	First admissions	0.24 (Africans) 0.14 (Indian Hindus) 0.09 (Indian Moslems)
Lin et al. (1989)	Taiwan	Three communities (n=39 024)	Household survey	0.17
Rajkumar et al. (1993)	India	Area in Madras (n=43 097)	Door-to-door survey and key informants	0.41
Hickling & Rodgers-Johnson (1995)	Jamaica	Total population (n=2.46 mln)	First contacts	0.24 ('broad') 0.21 ('restrictive')
Mahy et al. (1999)	Barbados	Total population (n=262 000)	First contacts	0.32 ('broad') 0.28 ('restrictive')

Table 3 WHO ten-country study: annual incidence rates per 1000 population at risk, age 15–54, for ICD–9 ('broad') and a 'restrictive' case definition of schizophrenia

Country	Area	'Broad' definition (ICD-9)			'Restrictive' definition*		
		Male	Female	Both sexes	Male	Female	Both sexes
Colombia	Cali	0.14	0.06	0.10	0.09	0.04	0.07
Czech Republic	Prague	0.06	0.12	0.09	0.04	0.08	0.06
Denmark	Aarhus	0.18	0.13	0.18	0.09	0.05	0.07
India	Chandigarh (rural area)	0.37	0.48	0.42	0.13	0.09	0.11
India	Chandigarh (urban area)	0.34	0.35	0.35	0.08	0.11	0.09
Ireland	Dublin	0.23	0.21	0.22	0.10	0.08	0.09
Japan	Nagasaki	0.23	0.18	0.21	0.11	0.09	0.10
Nigeria	Ibadan	0.11	0.11	0.11	0.09	0.10	0.10
Russia	Moscow	0.25	0.31	0.28	0.03	0.03	0.02
UK	Nottingham	0.28	0.15	0.24	0.17	0.12	0.14
USA	Honolulu, HA	0.18	0.14	0.16	0.10	0.08	0.09
USA	Rochester, WA	0.15	0.14	0.15	0.09	0.08	0.09

* Diagnosis of 'nuclear schizophrenia' assigned by the computer algorithm CATEGO [75] on the basis of symptoms subsequently incorporated into the ICD-10 diagnostic criteria for schizophrenia

schizophrenia were a subset of the cases of 'broad' schizophrenia, greater scatter and wider confidence intervals could be expected to characterise the 'nuclear' rates. However, this was not the case, suggesting that 'nuclear' schizophrenia is more homogeneous and occurs at a very similar frequency in the different populations. In recent years, replications of the design of the WHO ten-country study using the same instruments and procedures have been carried out with very similar results by investigators in India (Rajkumar et al. 1993), the Caribbean (Hickling & Rodgers-Johnson 1995; Mahy et al. 1999), and the United Kingdom (McNaught et al. 1997; Brewin et al. 1997).

Age

There is evidence that the risk of inception of schizophrenia extends beyond the age cut-off at 54 or 59 years. A major effect of the inclusion of late-onset schizophrenia (onset after age 40) and late paraphrenia (onset after age 60) in epidemiological studies would be a change in the sex ratio in lifetime prevalence estimates [the M:F becomes 1:1.9 after age 40 and 1:4 or even 1:6 after age 60 (Bleuler 1972; Huber et al. 1979)]. Each successive developmental stage seems to imprint differently the presenting clinical symptomatology, resulting in a predominance of non-specific psychotic symptoms in age groups 15–24; of delusions of reference and affective symptoms in age 25–34; and of persecutory delusions and negative symptoms in age 35–59 (Häfner et al. 1993). Although the presenting features of late-onset schizophrenia may vary from those of early-onset schizophrenia, there is no real 'point of rarity' between the two conditions and there is little support for the proposition that they are aetiologically separate disorders (Castle & Murray 1991).

Sex differences in age at onset

Sex differences in schizophrenia manifest themselves in several different ways: a lower age at onset and more frequent occurrence of brain abnormalities in men; better premorbid functioning, less disability and higher percentage of remitting course in women (Angermeyer et al. 1990; WHO 1979; Jablensky et al. 1992). However, there is no evidence of significant sex differences in the symptom profile of schizophrenia and in particular in the frequency of positive and negative symptoms (Häfner et al. 1993).

The earlier age at onset of schizophrenia in men has been reported since the beginning of the century. Hambrecht et al. (1992) re-analysed Danish and German case register data on first admissions with schizophrenia, as well as data from the WHO ten-country study. They found a marked male-female difference of 4–5 years in the mean age at first hospitalisation in Germany and Denmark, and a smaller but significant difference (mean 3.4 years) in the WHO study. However, other findings argue against the invariance of any such sex differences in age at onset. Such male-female differences in the age at onset are not observed among siblings in multiply affected families (DeLisi 1992). In some cultures, the trend may be non-existent or reversed. A study in India, on 200 consecutive admissions with first onset of schizophrenia documented such a reversal with a greater proportion of women developing schizophrenia at an earlier age than men (Murthy et al. 1992). A re-analysis of the WHO ten-country data using generalised linear models to unconfound the effects of gender, premorbid personality, marital status and family history of psychosis on the age at onset resulted in a significant attenuation of the sex difference, once the effects of other variables were removed (Jablensky & Cole 1997). Generally, sex differences in the age at onset, brain ab-

normalities and course of schizophrenia seem to reflect normal sexual brain dimorphism, rather than a sex-linked aetiological factor.

Course and outcome

Systematic investigations of the course and outcome of schizophrenia were initiated by Kraepelin (1919) who believed that the natural history of the clinical syndromes could provide a provisional measure of validity of the disease concept until final verification could be achieved by establishing the brain pathology and aetiology. However, longitudinal studies have highlighted a striking variability of the course of schizophrenia. Notwithstanding the possible effects of bias in many such studies due to the inclusion of patients at different stages of disease progression; overrepresentation of chronic cases in hospital samples; or exclusion at the start of the observation of patients with diagnoses other than schizophrenia who subsequently become re-diagnosed as schizophrenic, the evidence is consistent and points in the same general direction.

Longitudinal research in the past decades has added data corroborating the pattern outlined by earlier studies. With greater length of the follow-up the proportions of patients who are reported as improved or recovered tend to increase, e. g. from 10 % at the $2^1/_2$-year follow-up to 17 % at 5 years (Carone et al. 1991) and to nearly 60 % at the end of a 32-year follow-up (Harding et al. 1987). The same trend was observed in the International Pilot Study on Schizophrenia (WHO 1979; Leff et al. 1992), the WHO ten-country study (Jablensky et al. 1992) and the WHO Study on Assessment of Psychiatric Disability (Jablensky et al. 1980; Schubart et al. 1986). More recent, long-term follow-up findings from WHO centres participating in this collaborative research confirm the trend (Sartorius et al. 1996).

Population differences in outcome

Perhaps the most important finding of the WHO follow-up studies concerns a difference in the course and outcome of schizophrenia between 'Western' and 'Third World' populations. Earlier reports based on small clinical samples have pointed to a less disabling course and a high rate of recovery from schizophrenic psychoses in developing countries such as Mauritius (Murphy & Raman 1971) and Sri Lanka (Waxler 1979), even in cases with symptoms of potentially severe schizophrenia according to 'Western' prognostic criteria. However, selection bias could not be ruled out since the studies were based on hospital admissions; standard assessment procedures and explicit diagnostic criteria were not used; and clinical improvement could have been confounded with the good social adjustment some patients may achieve in a comparatively undemanding environment. The WHO International Pilot Study of Schizophrenia (WHO 1979) employing standardised assessment and more refined measures of course and outcome indicated that significantly higher proportions of the patients in India, Colombia and Nigeria had better outcomes on all measures than patients in the developed countries. For example, the initial psychotic illness had remitted during the 5-year follow-up in as many as 42 % of the patients in India and 33 % of the patients in Nigeria, whereas the majority of patients in the developed countries had experienced frequent relapses, persisting psychotic symptoms and disablement. Patients with good and poor outcome could not be distinguished on the basis of initial symptoms and they all met the ICD criteria for a diagnosis of schizophrenia. In the subsequent WHO ten-country study (Jablensky et al. 1992) potential cases were assessed at their first contact with community services. The sample included 586 patients in India, Nigeria and Colombia, of whom over 20 % were rural residents. The 2-year follow-up confirmed the finding that the outcome of schizophrenia was generally better in the developing countries than in the developed countries (Table 4).

Table 4 Two-year course and outcome features of 1070 patients with schizophrenia in the WHO ten-country study

Course and outcome measures	% patients in developing countries[1] (n = 467)	% patients in developed countries[2] (n = 603)
Remitting, complete remissions	62.7	36.8
Continuous or episodic, no complete remission	35.7	60.9
Psychotic < 5 % of the follow-up	18.4	18.7
Psychotic > 75 % of the follow-up	15.1	20.2
No complete remission during follow-up	24.1	57.2
Complete remission for > 75 % of the follow-up	38.3	22.3
On antipsychotic medication > 75 % of the follow-up	15.9	60.8
No antipsychotic medication during follow-up	5.9	2.5
Hospitalised for > 75 % of follow-up	0.3	2.3
Never hospitalised during follow-up	55.5	8.1
Impaired social functioning throughout follow-up	15.7	41.6
Unimpaired social functioning > 75 % of follow-up	42.9	31.6

[1] Colombia, India, Nigeria

[2] Czech Republic, Denmark, Ireland, Japan, Russia, UK, USA

The better overall pattern of course and outcome in the developing countries was mainly due to a significantly greater percentage of patients remaining in a stable remission of symptoms over longer periods after recovery from acute psychotic illness, and not to fewer or shorter psychotic episodes. The pattern was significantly predicted by setting (developing country), acute onset, being married or cohabiting with a partner, and having a supportive network (close friends). Being female was generally associated with a more favourable outcome. The length of remission was unrelated to pharmacological maintenance treatment which was only administered to a small proportion of patients in the developing countries. Independently of the WHO studies, a high proportion of better outcomes in schizophrenia in developing countries has been reported by numerous investigators (Kulhara & Chandiramani 1988; Ohaeri 1993; Thara et al. 1994).

The factors underlying the better outcome of schizophrenia in developing countries remain essentially unknown but are likely to involve interactions between genetic variation and specific aspects of the environment. Differences in the course and outcome of a disease across and within populations may be related to varying frequencies of predisposing or protective alleles coding for proteins involved in neurotransmitter regulation or stabilising the membrane of nerve cells. While such genetic differences undoubtedly exist, nothing specific can at present be said about their role in the course and outcome of schizophrenia. On the other hand, a strong effect of the psychosocial environment is entirely plausible, considering the contrasts between developing and developed countries with regard to social support systems, kinship networks and beliefs about mental disease (Warner 1985).

Contributions of epidemiology to risk factors and vulnerability markers

Schizophrenia as a complex genetic trait

Genetic vulnerability plays an important role in the causation of schizophrenia. A person's risk of developing schizophrenia increases steeply with the degree of genetic relatedness to an individual who has the disease. The twin concordance rate is close to 50% for monozygotic twins but only 10–15% for dizygotic twins, i.e. practically no different from the risk for full siblings. Follow-up studies of children adopted away early have shown that their risk of developing schizophrenia as adults is predicted by having (or not having) a biological parent with schizophrenia rather than by the characteristics of the adoptive family. The pattern of occurrence of schizophrenia in families is not compatible with the transmission of a single gene and it is likely that several or multiple genes are involved, each having a relatively small effect on the liability to develop schizophrenia (Kendler & Diehl 1993). The observation that the concordance rate for schizophrenia in genetically identical individuals such as monozygotic twins is no greater than 50% suggests that having the predisposing genes is not sufficient for the development of clinical disease. Such genes may remain 'silent' or unexpressed, unless some other factor – most likely an environmental one – triggers their activity. Many environmental exposures have been examined as possible risk factors, ranging from complications of pregnancy and birth to early viral infection, head injury, toxins or psychosocial adversity. None of these has been unequivocally validated and it is possible that different environmental exposures may interact with the predisposing genes at different developmental stages. These features place schizophrenia into the group of genetically complex diseases (Risch 1990), along with diabetes, cancer and hypertension, which have a polygenic basis; are heterogeneous (in the sense that different sets of genes may be involved in different populations or families); and whose causation involves environmental factors.

Maternal influenza

Following a series of reports on a statistical association between fetal exposure to maternal influenza during the second trimester of gestation and increased risk of schizophrenia in adult life, the issue remains controversial, with an increasing number of non-replications of the presumed link. Logistic regression analysis of the England and Wales data set (which had provided initial support for the hypothesis), failed to detect any significant association between in utero exposure to influenza epidemics and the paranoid schizophrenia when sex, season of birth and birth period were included in the analysis (Grech et al. 1997). Selten et al. (1998), using case register data to test the hypothesis that exposure to the 1957 A2 pandemic may have contributed to the high rate of schizophrenia among immigrants, also came to negative conclusions. A case register study on the first admission incidence of schizophrenia, affective psychoses, neurotic depression and mental retardation, in relation to six influenza epidemics in Western Australia 1950–1960 (Morgan et al. 1997), found no significant association except for a first and second trimester effect in mental retardation. Considering that studies in which investigators had access to individual women's records on influenza in pregnancy (Crow & Done 1992) have produced negative results, the case for any role of maternal influenza appears to be weakened, although a number of confounding factors might be masking a true effect. Ecological studies may never provide the solution and both innovative designs and informative databases are needed.

Pregnancy and birth complications

Obstetric complications remain a "hot area" of research into risk factors (Cannon 1997). Recent methodological refinements in this area include an increasing utilisation of prospectively recorded obstetric information and better procedures of aggregating and scaling pregnancy and birth data.

Results of considerable interest have emerged from a

meta-analysis of data on 854 individual patients (47.8 % of them rated as positive for OC), contributed by 11 European research groups (Verdoux et al. 1997). Using logistic regression and taking into account the effects of family history of psychosis and gender, the authors report a significant association (OR 1.52; 95 % CI 1.04–2.22) between an earlier age at onset and OC but not between age and onset and either family history or gender. The relationship between OC and age at onset tended to be linear and, therefore, suggestive of a causal effect. In another recent study, Hultman et al. (1997) scored the obstetric records of 107 consecutive admissions with schizophrenia or other non-affective psychotic disorders and of 214 controls. The group of schizophrenic and other psychotic patients was characterised by high gestational non-optimality scores corresponding to an odds ratio of 3.67 for schizophrenia and 4.58 for all psychoses combined. The summary non-optimality score was mainly influenced by gestational factors, in particular aberrant bodily size (disproportionately high or low body weight for body length, and a small head circumference). A range of factors, including placental insufficiency and infection, may result in retarded intrauterine growth. Accelerated growth, on the other hand, can be the result of hormonal influences.

Perinatal brain damage

Jones et al. (1998) reported findings from the North Finland birth cohort study in which 11 017 individuals have been followed up from late gestation to the end of their 27th year. Since prospectively collected data on maternal risk factors and on pregnancy, delivery, per- and postnatal complications were available, early antecedents of schizophrenia could be identified by case-control comparisons. The most significant finding was of a sevenfold excess (adjusted odds ratio of 6.9) among schizophrenic patients of perinatal brain damage which could account for a population attributable fraction of about 7 % of all cases of schizophrenia in the general population.

Early CNS infection

The Finnish cohort study also examined the effects of postnatal and early childhood CNS infection (using diagnoses confirmed by laboratory findings) on the risk of schizophrenia in later life. A significant association was found with viral infection, particularly with Coxsackie B5 meningitis in the neonatal period (Rantakallio et al. 1997).

Premorbid social adjustment

A large cohort study by Malmberg et al. (1998) involving a 15-year follow-up of 50 087 men conscripted into the Swedish Army in 1969–1970 at age 18–20, provided suggestive evidence that relatively common behavioural and cognitive traits in childhood and adolescence may be related to a predisposition to schizophrenia. Four variables reflecting social adjustment during childhood and adolescence (having fewer than two friends, preference for socialising in small groups, feeling more sensitive than others and not having a steady girlfriend) were significantly more common among the 195 individuals who subsequently developed schizophrenia as compared to the rest of the cohort. Positive scores on all four items resulted in a strikingly high odds ratio of 30.7 (CI 12.9–73.8) for schizophrenia, after adjustment for possible confounders. However, since these characteristics are widely prevalent in the population and a high proportion of the cohort scored positive on at least one item, the predictive value of this set of variables was extremely low: only 3 % of those who were positive on all four items developed schizophrenia during the subsequent 15 years. These findings are broadly in accord with earlier reports from the British 1946 birth cohort (Jones et al. 1994) which indicated that anxiety in social situations, solitary play preference, speech difficulties and low educational test scores in childhood and adolescence were significantly associated with adult schizophrenia.

Premorbid intelligence (IQ)

In a related analysis of the same cohort data, David et al. (1997) compared the performance on IQ-related tests and tasks at conscription of the 195 subjects who subsequently developed schizophrenia, 192 subjects who developed other psychoses, and the rest of the cohort. After controlling for confounding effects, the risk of schizophrenia increased linearly with the decrement of IQ (compared to an IQ > 126 as the baseline, the OR increase from 3.5 for IQ 90–95 to 8.6 for IQ < 74). The effect was mainly attributable to poor performance on verbal tasks and tests of "mechanical" reasoning.

Epilepsy

In a record-linkage study merging data from two Danish registers, Bredkjær et al. (1998) found highly significant associations between a diagnosis of epilepsy and a subsequent diagnosis of any non-organic, non-affective psychosis (OR 2.30). The association was particularly strong for psychomotor epilepsy and any psychosis in men (OR 5.07) and for psychomotor epilepsy and schizophrenia in men (OR 2.56). The study supports the notion that epilepsy, and in particular temporal lobe epilepsy, is a risk factor for non-affective psychosis including schizophrenia.

The nature of environmental influences

No major environmental factor in schizophrenia has yet been discovered. The emerging pattern of risk factors and antecedents of adult schizophrenia is one of multiple, mainly quantitative deviations from the average developmental trajectory, primarily in the areas of early neurode-

velopment, cognitive ability and social behaviour. The observed deviations are compatible with the notion of non-specific background factors facilitating the operation of specific causal pathways. Their effects may not be restricted to schizophrenia and could underlie a broad spectrum of psychosis.

Unexplained findings in the epidemiology of schizophrenia

High rates in immigrant groups

Exceptionally high prevalence and incidence rates of schizophrenia in second-generation Afro-Caribbeans migrants, i. e. those born in the United Kingdom, have been described since 1967 (Hemsi 1967). It now seems that the phenomenon cannot be fully attributed to diagnostic bias, misclassification or a lower admission threshold (Wessely et al. 1991). The causes of the Afro-Caribbean phenomenon remain obscure. Incidence studies in the Caribbean do not indicate any excess morbidity in the indigenous populations from which migrants are recruited. Little support has been found for explanations in terms of exposure to biological risk factors. No increase in the rate of pregnancy and birth complications was found in a case-control study (Hutchinson et al. 1997) and the suggestion that maternal exposure to the 1957 influenza pandemic might explain the excess morbidity has not been supported. However, studies which reported a significantly increased risk of schizophrenia for siblings of second-generation Afro-Caribbean probands but not for their parents (Hutchinson et al. 1996) suggest that an unknown environmental factor may be involved. Psychosocial influences, such as stress and demoralisation due to racial discrimination or thwarted opportunities have been considered but are yet to be translated into measurable variables.

Although the epidemiological evidence is weakened by the lack of reliable denominator data on the size and age structure of the Afro-Caribbean population in the United Kingdom (Harrison 1990), the reported risk elevation is of a magnitude that cannot be discounted. These, and similar data on immigrants from Surinam and the Dutch Antilles in the Netherlands (Selten et al. 1997; 1998), may provide important clues to risk factors in schizophrenia.

Urban birth

Urban environments have been thought to increase the incidence of psychosis either by directly contributing to causation (the "breeder" hypothesis) or by attracting vulnerable individuals (the "drift" hypothesis). Evidence for the latter was first proposed by Faris and Dunham (1939). There has been a recent revival of interest in the "urban factor". In a re-analysis of material from the US 1880 census of "insanity", Torrey et al. (1997) concluded that urban residence had been associated with an odds ratio of 1.66 for psychosis, compared to rural areas as the baseline. Marcelis et al. (1998) analysed all first admissions for schizophrenia and other psychoses in Holland between 1942 and 1978 by place of birth and found a statistically significant, linear relationship between size of urban areas and incidence rates of schizophrenia, affective psychoses and other psychoses. The size of this effect tended to increase in successive birth cohorts. However, no distinction could be made between effects attributable to urban birth (i. e. to a factor operating pre- or perinatally) and effects attributable to urban residence (i. e. to factors operating during postnatal development). Although the suspected "urban risk factor" is more likely to be ecological rather than genetic, a broad range of possibilities related either to the physical environment or to lifestyle and social factors need to be considered.

Season of birth

Fluctuations in the incidence of schizophrenia related to season of birth have been reported over nearly seven decades, and the majority of Northern hemisphere studies suggest a winter-spring excess. In a review of some 250 published studies, Torrey et al. (1997) concluded that notwithstanding methodological shortcomings, especially as regards the sample size needed, the evidence is consistent and points to a 5–8 % spring-winter excess of schizophrenia births. Seasonal excess was also found in bipolar disorder, major depression, autism and, possibly, in eating disorders and antisocial personality disorder. Statistical artifacts could not fully account for the findings. As regards the possible explanatory models, the field is almost limitless but no major advances have been reported. It seems unlikely that in the absence of a biologically plausible, testable causal hypothesis this avenue of research will advance aetiological knowledge much further.

Declining incidence of schizophrenia

Epidemiological evidence that real decreases may have occurred in the population frequency of schizophrenia over a period of several decades was first provided by the two census surveys on the island of Bornholm in 1935 and 1983 (Bøjholm and Strömgren 1989), which documented a decline of prevalence from 4.2 to 2.7 per 1000 in females but not in males. The possibility that the incidence of schizophrenia may be decreasing has more recently been raised by studies reporting significant declines of first admissions with schizophrenia according to national statistics. Should a true decline in incidence be demonstrated, there will be a case for a major environmental factor influencing the rates of the disorder. However, the data remain inconsistent or conflicting. Two studies (Jeffreys et al. 1997; Brewin et al. 1997) provide prevalence and incidence data on urban areas that had been surveyed 5 years earlier (inner London) and 12 years earlier (Nottingham). The point prevalence in Hampstead increased from 4.7 per 1000 in 1986 to 5.1 per 1000 in 1991 but the 5-year interval between the two surveys may be

too short for detecting any long-term trend. The Nottingham study compared two first-contact incidence cohorts, one assessed in 1978–80 and another in 1992–94, using essentially identical research procedures. All 1978–80 cases (with ICD-9 diagnoses) were re-diagnosed according to ICD-10 for comparison with the 1992–94 cohort. The rate of ICD-10 schizophrenia in 1992–94 was lower than 12 years earlier (0.87 as compared to 1.4 per 10000) but the shortfall matched a concomitant increase in 1992–94 of cases diagnosed as delusional disorders, acute psychoses, and drug-related psychoses. It is likely, therefore, that the decrease in ICD-10 schizophrenia between the two surveys reflects changes in the diagnostic patterns rather than a true decline in the population incidence of the disorder. No study to date has taken into account all possible confounding factors, such as changes in the definition of first admission or first contact; in diagnostic practice (e. g. a tendency to defer a diagnosis of schizophrenia on first admission); in treatment modality (an increasing number of patients being managed on an outpatient basis without admission to hospital); or in the age structure of the population, which may affect the rates if no standardisation for age is carried out. As a corollary, a compensatory increase could be expected in diagnoses other than schizophrenia. Such increases have actually been reported for borderline states (Munk-Jørgensen 1986) and for affective psychosis (Geddes et al. 1993). The question whether schizophrenia is becoming rarer remains open.

Conclusion: a research agenda

Epidemiological evidence now supports the conclusion that schizophrenia occurs universally and has similar manifestations and age and gender patterns in different populations. However, the extent and nature of the genetic, neurodevelopmental and environmental contributions to its etiology remain elusive. Epidemiological research in the past decade has mapped areas where potential clues might be found. Resolving, one way or another, contentious issues such as seasonality of births, the role of viral or obstetric developmental lesions, the excess incidence in second-generation migrants, and the possible decline in incidence, is a clear priority for the next few years. In the longer term, the research strategies which hold the best promise for new insights are likely to focus primarily on the population distribution and behavioural effects of potential risk factors and markers suggested by biological and genetic research rather than designs based on limited clinical samples. It is increasingly probable that the developmental antecedents and risk factors implicated in schizophrenia are not restricted to the diagnostic categories of DSM-IV and ICD-10 but underlie a broader spectrum of morbidity. Should this be the case, a prospect for epidemiological research would be to study the population distribution of "correlated phenotypes" such as neurocognitive deficits (Goldberg & Gold 1995) or other quantitative traits associated with the liability to psychosis. It is increasingly clear that the referents of the concept of schizophrenia reside in fundamental aspects of the organisation of the human brain, cognition and social communication. Until recently, these ideas have not been accessible to empirical research. Neuroscience is at present making inroads into this complex field. In due time, this may provide the basis for a molecular epidemiology of the psychoses as predisposing genotypes identified by quantitative traits or association studies. It would, therefore, be premature to engage in grand theory building about the nature and causes of schizophrenia; instead, we should aim to enlarge the scope and improve the quality of the knowledge base that would allow psychiatric research to draw on the new concepts and tools emerging in neuroscience, genetics and evolutionary biology.

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