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NEUROEPIDEMIOLOGY

Schizophrenia

Mary Cannon, Peter Jones

Psychiatric epidemiology is the study of the distribution and causes of mental disorder in the population. Over the past 30 years progress in psychiatric epidemiology has been slower than in other areas—for example, cardiovascular disease or cancer epidemiology, because of certain methodological problems that are just now being overcome. In particular the epidemiology of schizophrenia has suffered from two major difficulties: uncertainty about how to define a case, and the relative rarity of schizophrenia in the population.

Special methodological problems in schizophrenia epidemiology

WHAT IS A CASE

The lack of physical signs or laboratory tests means that a diagnosis of schizophrenia is based on evaluation of patients' self reported, subjective experiences. Until the late 1960s, there was a relatively loose definition of schizophrenia and a good deal of diagnostic latitude was allowed to individual psychiatrists. However, a report published in 1972,[1] showed that the diagnostic habits of psychiatrists in the United States and United Kingdom differed to an unacceptable degree, and led to the introduction of strict operational diagnostic criteria for schizophrenia. The Diagnostic and Statistical Manual DSM-III,[2] published in 1980, reduced the reliance on symptoms alone by incorporating an element of chronicity—six months prior duration of symptoms and an upper age limit of 45 years for a first diagnosis of schizophrenia. Since 1980 there have been two more restrictive revisions of this diagnostic system, DSM-III-R[3] and DSM-IV,[4] and the International Classification of Diseases, (ICD), the diagnostic system favoured by European psychiatrists, has also undergone a similar "narrowing" process with the change from ICD-9 to ICD-10.[5]

But has this process gone too far? Although the restrictive diagnostic criteria have certainly increased the *reliability* of the diagnosis, they have not improved the *validity* of "DSM-IV" or "ICD-10 schizophrenia".[6] Recent family studies indicate that a broader concept of schizophrenia actually fits genetic models more readily than a restrictive definition. In addition, the frequent changes in diagnostic criteria have affected the comparability of studies of time trends and outcome in schizophrenia. Also, the commitment to a phenotype based on symptoms in adult life may have ignored an important developmental or lifelong dimension to the disorder.

SCHIZOPHRENIA AS A "RARE DISEASE"

The low incidence (10–40 cases per 100 000 per year) and relatively low lifetime prevalence (0·5%–1%) of schizophrenia in the population have led to a reliance on case-control study designs in research. Chronic patients recruited from hospital wards are compared with volunteer controls from the community and consequent problems of bias and confounding have often led to unreplicated and contradictory findings. It seemed for a time that schizophrenia, already known as the "graveyard of neuropathologists",[7] would also prove to be the undoing of epidemiologists. Over the past two decades, however, the application of advances in case-control methodology to psychiatric epidemiology has led to more robust results.[8] Also, cohort designs, for long thought too costly and time consuming to use in schizophrenia research, have made a "comeback".

For the purposes of this review schizophrenia refers to a recent, operational definition such as CATEGO,[9] ICD-10, DSM-III, DSM-III-R, or DSM-IV. Robust findings are those from studies with an epidemiological design—that is, population based studies with well defined samples and appropriate controls. We aim to show how the findings from robust epidemiological research can help to unravel the complex aetiology of schizophrenia.

Geography

In 1978, a large multicentre study of schizophrenia was initiated by WHO—the 10 country study (also known as the Determinants of Outcome of Severe Mental Disorders Study), to provide information about the incidence, course, and outcome of schizophrenia in different cultures.[10] Two case definitions of schizophrenia were used: a broad, clinical definition comprising ICD-9 schizophrenia and paranoid psychoses, and a narrow, restrictive definition including only cases classified as "nuclear" schizophrenia using the CATEGO computer programme [9] Figures 1A and B show the incidence rates for both definitions.

Department of Psychological Medicine, Institute of Psychiatry, Denmark Hill, London SE5 8AF, UK
M Cannon

Department of Psychiatry, University of Nottingham, Duncan Macmillan House, Porchester Road, Nottingham NG3 6AA, UK
P Jones

Correspondence to:
Dr Peter Jones.

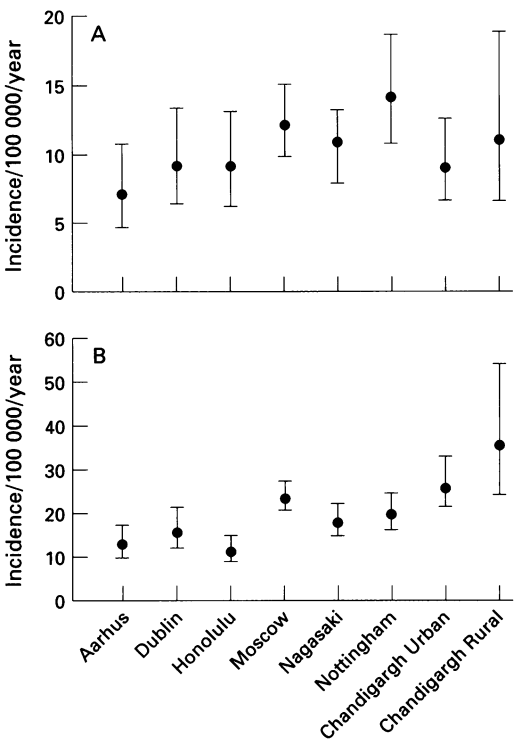

Figure 1 (A) Incidence of CATEGO S narrow schizophrenia with 95% confidence intervals from eight centres in the WHO Determinants of Outcome Study. (B) Incidence of CATEGO S, P, and O broad schizophrenia with 95% confidence limits from eight centres in the WHO determinants of outcome study. Data from Jablensky et. al.[10]

There is little variation between centres for narrowly defined schizophrenia with rates ranging only between 7 and 14/100 000, (fig 1A). Although the parsimonious conclusion would be that the rates for narrowly defined schizophrenia are the same, the confidence intervals for these estimates were wide and there may not have been sufficient statistical power to detect differences.

The incidence rates for broadly defined schizophrenia do seem to vary between countries (range 16 to 42/100 000 per year), and the rates for centres in the developing world are about twice as high as those in the developed world (fig 1B). Further studies of schizophrenia in the developing world are needed to replicate and further investigate these interesting findings, and the problem of mental health in the developing world can no longer remain a low priority for funding agencies and governments. On the whole, however, the variation in incidence rates for schizophrenia world wide is very small compared with illnesses such as ischaemic heart disease or cancer, which are known to have major environmental risk factors.

Time trends

PREVALENCE DATA

Two major prevalence studies of psychiatric illness have been carried out in the United States, which indicate a decrease in prevalence of schizophrenia over one decade. The Epidemiological Catchment Area (ECA) Study surveyed 17 803 persons between 1980 and 1984 and found a lifetime prevalence of schizophrenia of 1·4%.[11] The National Comorbidity Survey (NCS) interviewed 8098 people between 1990 and 1992 and found that lifetime prevalence for the summary category of non-affective psychosis was 0·7%.[12] This discrepancy may be related to issues of sampling, interview methodology, or actual change over time and remains to be clarified by future reports.

A major prevalence study of psychiatric morbidity carried out in the United Kingdom between April and September 1993,[13] found a prevalence rate of 0·4% for functional psychosis among persons aged 16–64 living in private households. This rate is even lower than that found in the national comorbidity survey but as 37% of those who screened positive for psychosis refused a second diagnostic interview, the true prevalence may be higher.[14] At present, it seems that the lifetime prevalence of schizophrenia in the western world lies somewhere between 0·4% and 1·4%, and may have decreased over the past decade.

"INCIDENCE" DATA

Prevalence of schizophrenia can be influenced by factors such as change in treatment, change in mortality rate, and changes in the age and sex structure of the population, and therefore, examination of incidence rates may be more informative. Ideally, such studies should be based on community incidence samples but, as this is difficult to achieve, case registers and hospital admission data are commonly used.

Eagles and Whalley[15] first reported a decline in the diagnosis of schizophrenia among first admissions in Scotland between 1969 and 1978. There have since been 14 papers examining this issue in England,[16–20] Scotland,[21–23] Denmark,[24 25] New Zealand,[26] Canada,[27] Ireland,[28] the United States,[29] and the Netherlands.[30] Those based on national statistics have found a large (40%–50%) decline in first admission rates for schizophrenia during the 1970s and the 1980s.[17 18 25 26] Findings based on case register data have been less consistent and indeed, two such studies, from Camberwell[17] and Salford[18] in the United Kingdom, actually found a slight increase in the incidence of schizophrenia during the same period. Others have reported a decrease in first admission rates for schizophrenia among female patients only.[22 28 30]

The major question is whether the decrease noted in first admission rates corresponds to an actual decrease in the incidence of the condition. Many factors influence this apparent "administrative decline" in schizophrenia: (1) The introduction of more restrictive diagnostic criteria for schizophrenia may cause a shift to diagnoses such as "borderline states"[24] or affective psychosis.[29 30] (2) The move to community care over the past two decades could have affected hospital admission rates.[27] (3) Clinicians have become more reluctant to make a diagnosis of schizophrenia on the first hospital admission,[24] and this could lead to a spurious fall in incidence rates over the last few years of the period under observation. The policies of private health insurance companies regarding schizophrenia may be partly responsible for this effect.[29] (4) Changes in the age, sex, and ethnic structure of the population over the period under study have not been

taken into account in most studies. The two areas of the United Kingdom which showed an increased incidence of schizophrenia are both areas with a high proportion of immigrants.[17 18] Unfortunately, schizophrenia has such a low incidence that it may be impossible to disentangle all these effects and reach any firm conclusions regarding changes in incidence in the developed world in recent decades.[31]

Characteristics of patients

AGE AND SEX DISTRIBUTION

Total lifetime risk for schizophrenia seems to be equal in both sexes.[10 32] Schizophrenia can occur at any age,[33-35] but onset is commonly in early adulthood—over 70% of incident cases in the WHO 10 country study were between 15 and 35 years of age.[10] The mean age of onset for male patients is three to four years earlier than for female patients, irrespective of whether onset of schizophrenia is defined as the first sign of mental disorder, the first psychotic symptom, or the first hospital admission.[36-38] The peak age of onset for males is between 15 and 30 whereas females have a slower and more even rate of onset with a peak between the ages of 20 and 35 and a second smaller peak after the age of 45, (fig 2).[38] No satisfactory explanation yet exists for this sex difference. A protective effect for female sex hormones has been suggested,[39] but has not been proved empirically. The same pattern occurs across countries indicating that it is not an effect of cultural factors.[10]

SOCIAL CLASS

The long recognised association between schizophrenia and low social class was confirmed by the ECA study, which showed that schizophrenic patients in the United States were 10 times more likely to be in the lowest socioeconomic group than in the highest.[35] Evidence from birth cohorts in Britain,[40 41] and Finland[42] show that this relation is not causal—schizophrenic patients at birth have the same socioeconomic distribution as the general population. What is remarkable is the steep decline in social state which accompanies the illness and is evident even before the clinical onset.[42 43] This decline is far greater than that experienced by patients with severe affective disorder.[42 43]

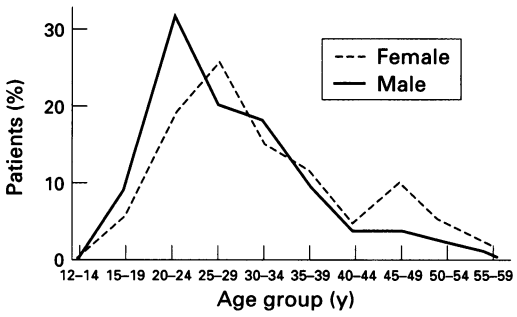

Figure 2 Distribution of age at first admission for schizophrenia in males and females. Source: Häfner et al.[38]

MARITAL STATE

Schizophrenic patients have low rates of marriage and low fertility[32]—a challenge to geneticists. Married patients have a better clinical and social outcome than single patients,[10] although marriage may, of course, reflect better premorbid social adjustment and later age at onset, which are both independent predictors of good outcome. However, the prevalence of schizophrenia among separated or divorced people in the United States (2·9%) is similar to that among single people (2·1%), suggesting that marriage may confer an independent protective effect.[32] An interaction between marital state and gender was found in the one year follow up of the ECA study.[44] Single women were 14 times more likely to develop schizophrenia than married women but single men were almost 50 times more likely to develop schizophrenia than their married counterparts. The role of marital state as a risk indicator or modifier for schizophrenia deserves further study.

ETHNICITY AND MIGRANT STATE

To date no single *indigeneous* ethnic group seems to have a significantly higher rate of schizophrenia than any other,[10] although some pockets of high prevalence may exist in isolated areas like north Sweden.[45] The west of Ireland[46 47] and the Istrian peninsula in Croatia[48] had previously been identified as high risk cultures but the higher rates originally found among these peoples are now thought to be due to methodological factors.[49] Populations with increased prevalence, if carefully identified, could be very useful for geneticists, but they seem to be local exceptions rather than the general rule in the epidemiology of schizophrenia.[50] The ECA study found a higher prevalence for schizophrenia among black people than among white people in the United States (2·1% v 1·4%).[32] However, when controlled for age, gender, marital state, and most importantly, socioeconomic group, the significant difference disappeared. Of course in a cross sectional study such as the ECA study, it is not possible to state definitively that current marital state and socioeconomic state completely explain the association found between race and disorder, because schizophrenia can lead to low social state and marital breakup.

Schizophrenia in immigrants

In 1988, the psychiatric community was surprised by a report that the incidence of schizophrenia among the Afro-Caribbean population in Nottingham was more than 10 times higher than in the general population.[51] This finding has been convincingly replicated in other centres in the United Kingdom[52-55] and in The Netherlands,[56] although the incidence ratio is now thought to be rather lower (3–5) when the denominator is adjusted for possible underreporting in census data.[54 55] An increased incidence ratio for schizophrenia has also been found among African[54 55] and Asian[54] immigrants in the United Kingdom, indicating that the effect is not confined to a single ethnic minority.

The hospital admission rate for schizophrenia among migrants is higher in their host country than in their country of origin,[57-59] which implicates factors occurring principally after migration. The risk of schizophrenia is greater among second generation migrants than first generation migrants,[51-54 60] arguing against selective migration of preschizophrenic persons. The fact that immigrants from poor countries tend to show higher rates of schizophrenia than immigrants from affluent countries, implies that factors associated with improved living conditions, industrialisation, or urbanisation are involved. Obstetric complications and exposure to novel viruses during pregnancy have been proposed as biological explanations,[61 62] but empirical evidence is lacking. One study has found an increased risk for schizophrenia among the siblings of United Kingdom born Afro-Caribbean schizophrenic patients compared with the risk among siblings of white patients,[63] which could indicate a gene-environment interaction effect.

Despite these intriguing clues, the evidence for a unique epidemic of schizophrenia among certain immigrant groups, although suggestive, is not conclusive. No studies have controlled adequately for possible confounders such as low socioeconomic class and marital state, which may reduce the incidence ratio even further. It is likely that ethnicity represents a "proxy" variable for various social and perhaps biological factors. Once these are controlled, there may be little or no residual effect of ethnicity itself but we would gain information about other, perhaps preventable, risk factors involved. The most parsiminious conclusion would be that schizophrenia in immigrants is caused by the same factors that cause schizophrenia in other groups but that these factors are more common, (and therefore more conspicious), after migration. The alternatives—that there are specific causes in immigrants which do not occur in other populations or that there is true interaction with ubiquitious factors causing schizophrenia in only some groups—both require further research.

COURSE AND OUTCOME

Outcome studies in schizophrenia are usually based on hospital treatment samples and may not be representative of the population of schizophrenic patients[64]; indeed, the true natural course of schizophrenia is almost always masked by treatment these days. The results of outcome studies are difficult to summarise because the definitions of outcome and methods of assessment used are so varied. However, all studies attest to the striking variability of course and outcome of schizophrenia.[64] At the extremes of outcome, 20% of patients seem to recover completely after one episode of psychosis,[65-68] whereas 14%–19% of patients develop a chronic unremitting psychosis and never fully recover.[10 65 69] In general, clinical outcome at five years seems to follow the rule of thirds: with about 35% of patients in the poor outcome category[65 69]; 36% in the good outcome category,[65 70 71] and the remainder with intermediate outcome. Prognosis in schizophrenia does not seem to worsen after five years.[50 71]

The effect of changes in diagnostic criteria has been highlighted in a recent meta-analysis of outcome studies over 100 years,[70] which found that prognosis for schizophrenia has worsened over the past decade. The more restrictive definitions of schizophrenia post-DSM-III, predict worse prognosis, partly as a "self fulfilling prophecy", as chronicity over six months is already built into the definition of the disorder.[6]

Predictors of course and outcome

Immutable factors—Patients from developing countries have a better outcome than patients from developed countries,[10 65] but it is not known which aspects of non-Western culture are responsible for this effect. Possible social factors are lower levels of expressed emotion,[72] stronger social support networks, or lack of stigma. Ethnicity may be related to outcome but conclusions are preliminary.[73] Other favourable prognostic factors are good premorbid social adjustment, female sex, being married, and later age at onset,[10 65] but these factors are unlikely to act independently.[74] Acute onset of illness and the experience of negative life events before illness are also related to better outcome.[65 75]

Mutable factors—High levels of "expressed emotion" among close relatives—namely, criticism, hostility and, overinvolvement[76 77]—predict early relapse. Substance misuse[10 78] also predicts poor prognosis. The important finding that delay in receiving treatment results in poorer outcome,[79-81] might be due to bias, and confounding with certain chemical characteristics resulting in delayed treatment, but it is possible that a more biological process is involved, with persistence of untreated positive symptoms altering the "hard wiring" in the brain.

MORTALITY

Standardised mortality ratios (SMRs) for schizophrenic patients are estimated to be two to four times higher than the general population,[82] and their life expectancy overall is 20% shorter than for the general population.[83] The most common cause of death (in 10% of patients), is suicide—the risk of suicide is 20 times higher than for the general population.[82 83] Young men with a chronic illness are at particular risk.[84] More work needs to be carried out to identify patients at risk of suicide, and to determine the effect of secular trends such as deinstitutionalisation on suicide rates. Deaths from heart disease and from diseases of the respiratory and digestive system are also increased among schizophrenic patients.[82 83] Certainly the lower socioeconomic status associated with schizophrenia carries with it many risk factors for physical diseases, such as smoking and poor diet, all of which are preventable.

Risk factors

Until recently, research into the aetiology of

schizophrenia focused principally on family relationships and social stressors. A remarkable "paradigm shift" has taken place over the past decade; schizophrenia is now considered to be a brain disease and emphasis is placed on biological determinants.[85] The impetus for this change came from neuroimaging and neuropathological studies showing evidence of brain abnormalities in schizophrenic patients.[86] The timing of these pathological changes is unclear but is likely to be a defect in early brain development.[86] Profound changes have also occurred in hypotheses concerning neurotransmitter abnormalities in schizophrenia. The dopamine hypothesis has been extensively revised and is no longer a considered a primary causative model—current research focuses on the interaction between different neurotransmitter systems.[87]

GENETIC FACTORS

Family studies

Schizophrenia runs in families. First degree relatives of schizophrenic patients have a morbid risk of developing schizophrenia which is 10 times higher than in the general population.[88 89] The excess risk of developing schizophrenia occurs principally among the children and siblings of patients. Parents are at lower risk of developing schizophrenia, probably because the low fertility associated with having schizophrenia means that parents are, of necessity, "selected for health", and have already survived much of the period of risk.[90] However, "familiality" of an illness does not necessarily indicate a genetic effect and can also be due to environmental factors. Adoption studies and twin studies allow these effects to be examined separately.

Adoption studies

Results from the influential Danish adoption study[91] show that the risk for schizophrenia among the biological first degree relatives of the schizophrenic adoptees is almost eight times higher than the risk among biological relatives of control adoptees.[92] Preliminary results from another large adoption study being carried out in Finland concur with these findings.[93] An increased risk of schizophrenia, in the absence of any contact with biological relatives, indicates that the familial aggregation of schizophrenia is due largely to genetic factors and not to some other aspect of the familial environment. Of course the adopted-away child has still spent the prenatal period with the biological mother and therefore prenatal environmental risk factors cannot be ruled out. However, the risk of schizophrenia spectrum disorders, (see below), was also increased in the paternal half siblings of the schizophrenic adoptees, who shared neither the prenatal nor familial environment.[91]

Twin studies

Twelve major twin studies of schizophrenia have been carried out, all of which show that the risk for schizophrenia in the co-twin of a schizophrenic proband (the *probandwise concordance*) is substantially higher for MZ than DZ twins.[94] Although the average probandwise concordance in MZ twins is 46% (compared with 14% in DZ twins),[95] the offspring of discordant MZ twins have *all* been found to share the same risk of developing the disorder,[96] raising the possibility that the unaffected MZ twin may represent an unexpressed genotype. Genetic factors are undoubtedly predominant but there is evidence (discussed below) that non-genetic factors may be involved in the aetiology of schizophrenia. The average estimate of the proportion of liability attributable to non-genetic factors in schizophrenia is 0·18.[94]

What is transmitted?

The "schizophrenia spectrum"—Certain psychiatric illnesses and personality disorders, known as the schizophrenia spectrum, are thought to be genetically linked to schizophrenia. The most important of these disorders is schizotypal personality disorder, and the relative risk for schizotypal personality disorder in the first degree relatives of schizophrenic probands compared with controls is about five.[97 98] Parents of schizophrenic patients have a higher risk of schizotypal personality disorder than siblings, suggesting that individuals who inherit this milder genetic vulnerability are responsible for the maintenance of schizophrenia in the population.[89] Within the cluster of symptoms and signs which comprise the diagnostic entity of schizotypal personality disorder—aloofness, poor rapport, social dysfunction, odd speech patterns, and avoidant symptoms in particular—predict genetic vulnerability to schizophrenia.[99]

Other disorders which form part of the schizophrenia spectrum are schizoaffective disorder,[100] paranoid personality disorder,[98] and schizoid personality disorder,[91 97] although there is some debate about the second.[98] No excess of anxiety disorder or alcoholism has been found in the relatives of schizophrenic patients compared with the relatives of controls, indicating that the genetic transmission of schizophrenia and schizophrenia spectrum disorders is relatively specific and does not include a generalised liability to all psychiatric illness.[91 97 101] The debate about whether affective disorders occur to excess in the relatives of schizophrenic patients has not yet been resolved,[88 101 102] although relatives of schizophrenic patients seem to have an increased predisposition to develop psychotic symptoms as part of an affective illness.[101]

DEVELOPMENTAL ABNORMALITIES

Evidence for developmental abnormalities in schizophrenia has come from two sources of prospective data: (*a*) high risk studies and (*b*) general population birth cohorts.

High risk studies

The high risk study design involves following up offspring of schizophrenic mothers until they have passed through the period of risk for schizophrenia. Only the Copenhagen high risk

study[103] has completed follow up of its probands, but because probands were recruited at age 15 there are no data on early development. The second generation of high risk studies in schizophrenia, which were started during the middle and late 1970s, began their observations on high risk children from the time of birth. The most influential of these studies are the New York High Risk Project,[104] the Jerusalem Infant Development Study,[105] and the high risk study of Barbara Fish.[106] As the subjects are now still in their teens and 20s, full information on outcome in the cohorts will not be available for another 10 years or so, but interesting data on infant and early childhood development among the high risk children have already been published and show a high degree of consistency between studies.

The developmental abnormalities found in 25%–56% of high risk children during different stages of childhood can be summarised as follows:

- *Neonatal period*: hypoactivity; extreme variation in alertness; hypotonia; poor "cuddliness"
- *Infancy*: a delay in acquisition of developmental milestones and a disordered pattern of acquisition of milestones—termed "pandysmaturation" by Fish[106 107]
- *Early childhood*: soft neurological signs, in particular poor motor coordination
- *Late childhood*: deficits in information processing and deficits in attention.

The question which remains to be answered is whether the children who have displayed these neurodevelopmental abnormalities throughout childhood will develop schizophrenia or a schizophrenia spectrum disorder in adulthood. Results from general population birth cohort studies (discussed below) and from a study based on examination of childhood "home movies" of schizophrenic patients[108] have replicated some of these developmental findings.

General population studies

Population based cohort studies can overcome the problem of generalisability associated with high risk studies. Unfortunately the information collected during childhood, although safe from selection and information bias, is often not ideal. In the United Kingdom, two such studies have now reported findings concerning schizophrenia.[40 41]

The National Survey of Health and Development, also referred to as the British 1946 birth cohort, comprises a sample of 5362 people born in the week 3–9 March 1946, who have been regularly followed up over four decades. Jones and colleagues[40] identified all cases of schizophrenia (30 in total) from this cohort and using the detailed, unbiased assessments made during childhood, investigated childhood developmental risk factors for adult schizophrenia in these patients using the remaining sample as a comparison group. Children who went on to develop schizophrenia as adults could be distinguished from their peers in the following ways:

- Motor development milestones, in particular walking, were delayed by an average of 1·2 months
- More speech problems (odds ratio/OR 2·8)
- Lower educational test scores at ages 8, 11, and 15
- Preference for solitary play at age 4 (OR 2·1)
- When the children were aged 4, health visitors rated the mother as having below average mothering skills and understanding of her child (OR 5·8): a finding which may indicate deviance in the child, the mother, or both.

The National Child Development Survey, also known as the British perinatal mortality survey, comprises all those born in the week 3–9 March 1958. Forty patients with schizophrenia were identified from this cohort. An investigation of childhood behavioural characteristics found that at the age of 7 patients were rated by their teachers as more socially maladjusted than controls.[41] Findings regarding low IQ were similar to the 1946 cohort.

These developmental findings are presumed to show differences in the way the brain is developing. Whether or not the developmental differences themselves modify risk, they have to be explained by any aetiological theory of schizophrenia, genetic or otherwise, and add a longitudinal aspect to the phenotype.

NON-GENETIC ENVIRONMENTAL RISK FACTORS

Birth complications

Case-control studies have found that schizophrenic patients as a group experience more birth complications than controls,[109] but studies may have been subject to many types of bias including recall, selection, and publication bias.[110] Three studies have used a cohort follow up design and have found modest increases in relative risk (about 2) for schizophrenia associated with certain birth complications: chronic fetal hypoxia,[111] low maternal weight,[112] and rhesus incompatibility.[113]

Place and time of birth

There is a small increase in risk for schizophrenia (OR 1·15), among people born in winter or early spring.[114] The reason for this season-of-birth effect is unknown, although it may be due to infectious diseases.[115] Being born in a city seems to be associated with a slight increase in risk for schizophrenia (OR 1·38), after adjusting for socioeconomic factors,[116] although not all studies have found such an effect.[40] Urbanisation, like social class, is a proxy measure for many other risk-increasing agents which are likely to operate synergistically.

Prenatal risk factors

Ecological studies have shown a modest increase in risk of schizophrenia (OR 2·0), associated with exposure to influenza in the second trimester of fetal life, particularly for the 1957 influenza epidemic.[117–119] Cohort follow up studies have had low power to examine this association,[120 121] and the case remains

unproved. Nutritional deficiency during the first trimester may also increase risk (OR 2·0).[122 123] One intriguing, although unreplicated, study from Finland found that the risk of schizophrenia was higher (OR 6·2) among offspring of women who lost their spouse during pregnancy than for those whose spouse died during the child's first year, possibly indicating that severe maternal stress can affect fetal development.[124]

Heavy cannabis intake

Heavy cannabis consumption at the age of 18 was associated with an increased risk, adjusted for confounders, of later psychosis (OR 2·3) in a large cohort of military conscripts in Sweden.[125] A dose-response relation was convincing but the direction of causality remains in question.

Cerebral ventricular enlargement

Small case-control studies have been the mainstay of neuroimaging research in schizophrenia and findings are remarkably contradictory.[126] It is likely that the previously mentioned problems of bias, confounding, and inadequate power are at least partly responsible. The most consistent finding is that schizophrenic patients have larger lateral cerebral ventricles than controls. The level of risk associated with ventricular enlargement, adjusted for intracranial volume, age, sex, ethnicity, and social class, is about 2·0, although the whole notion of categorical definitions of pathology in terms of enlargement or shrinkage has been challenged.[127]

RISK FACTORS AS CLUES TO AETIOLOGY

Examination of the effect sizes of various risk factors can give clues to causation. The table shows that only genetic risk factors come anywhere near the effect size expected for a strong causal agent in schizophrenia. However, the existence of so many environmental risk factors with small effect sizes cannot be ignored. These may be proxy measures for an as yet unrecognised major environmental causal agent, or may act additively with each other or with chance events. They could also indicate the existence of gene-environment interactions.

Best estimate sizes of various genetic and environmental risk factors for schizophrenia (expressed as odds ratios or relative risks)

Category of risk factor	*Specific risk factors*	*Best estimate of effect size*
Genetic*	MZ twin of schizophrenic patients	46
	Child of two parents with schizophrenia	40
	DZ twin of schizophrenic patient	14
	Child of one schizophrenic patient	10
	Sibling of schizophrenic patient	10
	Parent of schizophrenic patient	5
Developmental†	Delayed milestones	3
	Speech problems	3
	Cerebral ventricular enlargement	2
Postnatal environment†	Immigrant/ethnic minority status	5
	Chronic cannabis consumption	2
	Solitariness as child	2
Prenatal and perinatal environment†	Birth complications	2
	Severe undernutrition (1st trimester)	2
	Maternal influenza (2nd trimester)	2
	Born in city	1·4
	Born in winter/early spring	1·1

*Relative risks; †odds ratios

Gene-environment interaction

Traditional aetiological models have considered vulnerability to schizophrenia as the sum of the impact of genetic and environmental risk factors—an additive model. But the concept of *gene-environment interaction*—that is, genes controlling sensitivity to the disease—predisposing effects of the environment, can no longer be neglected,[128] with many examples being found in the fields of medicine[129] and psychiatry.[130]

Both psychosocial and biological environmental factors may interact with genetic vulnerability to increase the risk for schizophrenia. Initial results from the Finnish adoption study of schizophrenia show a greater risk of psychosis among the biological offspring of schizophrenic mothers who were placed in poorly functioning adoptive homes than among those in well functioning adoptive homes.[93] High risk children who were reared in a kibbutz had increased rates of schizophrenia in adulthood compared with those who were reared in family homes, whereas control (low risk) children reared in a kibbutz had no increased risk of psychopathology.[131] A series of analyses from the Copenhagen high risk study has shown that birth complications may interact with genetic factors to increase the risk of schizophrenia.[92 132 133]

In other words, the pathogenic effects of birth complications, an adverse adoptive home, or some aspect of life in a kibbutz seem to increase risk of schizophrenia only in children who already have some degree of genetic vulnerability. Although the evidence is preliminary, it indicates that the environment should no longer be considered a "nuisance variable" by psychiatric geneticists. Common environmental factors may work in combination with rare high risk genotypes to maintain schizophrenia in the population.

NEW STRATEGIES IN MOLECULAR GENETICS

The search for the "psychosis gene"[134] has met with substantial difficulties, including lack of a valid phenotype; the possibility of genetic heterogeneity; the possibility of environmental effects acting alone or in combination with genetic factors; and lack of knowledge about the exact mode of transmission.[94] Traditional linkage techniques are only able to exclude the existence of single major genes. As the genetic aetiology of schizophrenia is likely to be complex, involving genes of small effect, new techniques, and strategies are necessary.[90 94 134]

Linkage studies

Linkage strategies for detecting genes of small effect include non-parametric techniques, such as affected sib pair and affected relative pair approaches, which make no assumptions about mode of transmission. A recent variation on the sib pair design is the quantitative trait locus approach which involves measuring liability to schizophrenia as a continuous variable in siblings.[135 136] The application of the techniques of behavioural genetics to the study of schizophrenia is likely to prove a fruitful area for the future.[135]

After a false positive report of linkage on chromosome 5,[137] current interest centres on chromosome 22[138] and particularly on chromosome 6.[139] A large study of 265 Irish multiplex families has found evidence for linkage on chromosome 6p24-22 using a model assuming a broad phenotype and genetic heterogeneity.[139] This locus is thought to confer susceptibility to schizophrenia in 15%–30% of families studied.

Association studies

Allellic association studies, which compare the frequency of marker alleles in a sample of patients compared with ethnically matched controls, are another method useful for examining genes of small effect.[137] An association between HLA A9 and schizophrenia has been found, but this effect is weak (OR 1·6), and its significance is uncertain.[90] Another promising area for the future is the use of newly developed DNA polymorphisms to examine candidate genes (genes coding for proteins which are likely a priori to be involved in the pathogenesis of schizophrenia)—for example, genes involved in neurodevelopment.[140] This approach offers the possibility of elucidating the cause of schizophrenia at a cellular level, bridging the gap between epidemiology and the basic sciences.

Conclusion

Schizophrenia occurs in all countries and in all races. On the whole, there is little variation in incidence or prevalence between countries, but there seems to be an increase in the incidence of schizophrenia when populations migrate. The reason for this immigration effect is unknown and is currently the subject of intensive study in the United Kingdom. Schizophrenia is associated with considerable morbidity and high mortality, and more information is needed on predictors of suicide among patients. However, on the positive side, the clinical outcome is not as hopeless as previously thought—almost 20% of patients make a full recovery after the first episode of psychosis and there is suggestive, although not conclusive, evidence for a decrease in incidence in the developing world.

The aggregation of schizophrenia in families, the evidence from twin and adoption studies, and the lack of variation in incidence world wide, indicate that schizophrenia is primarily a genetic condition, although environmental risk factors are also involved at some level as necessary, sufficient, or interactive causes. The persistence of schizophrenia in the population despite low fertility and high mortality, suggests that genetic transmission occurs principally through persons who do not have the illness. Further refinement of the diagnostic concept of the *schizophrenia spectrum* in both cross sectional and longitudinal terms will help elucidate the mode of transmission, and reliable instruments must be developed to detect these disorders in the community.

Areas of particular interest for the future are studies of risk factors and developmental abnormalities in those with known genetic vulnerability for schizophrenia—for example, siblings; the use of new molecular genetic strategies—including behavioural genetics—and the study of gene-environment interactions. If current progress in epidemiological and genetic research in schizophrenia continues, it is likely that the aetiology of this complex disorder will at least begin to be unravelled before the "decade of the brain" is over.

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