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Editorial

What is Schizophrenia?

Changing Perspectives in Epidemiology

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Summary. The psychotic syndrome at the core of schizophrenia appears to be invariable across cultures. The risk of morbidity also seems to vary very little from country to country and over medium periods of time. Moreover, apart from gender differences in first onset, the cumulative lifetime risk is the same in females and males. A similar epidemiological pattern is only found in pathological conditions that are characterized by a precisely defined section of a psychopathological dimension with a continuous distribution in the population, e.g. severe mental retardation being the extreme section of normally distributed IQ values. The interpretation of schizophrenic psychosis as the extreme section of a psychopathological dimension or disposition that is almost evenly distributed in all populations is supported by the fact that milder psychiatric disorders occur more frequently before the onset of the psychosis and in close relatives of schizophrenic patients. The psychopathological heterogeneity of these disorders argues against the assumption of a manifest psychopathological dimension with a continuous transition from the schizophrenic psychosis to the "normal" schizothymic personality. More probable is a continuously distributed latent vulnerability to schizophrenia – with or without a threshold effect – which in severe degrees disposes to the uniform reaction pattern of the schizophrenia syndrome. Smaller degrees of vulnerability are associated with an increased risk for milder patterns of disturbances, which are also more strongly determined by environment and personality and therefore are rather heterogeneous. These assumptions lead to other epidemiological and genetic models than Kraepelin's early concept of a disease entity does.

Key words: Aetiology of schizophrenia – Epidemiology of schizophrenia – Disease concept of schizophrenia – Continuous model of vulnerability to schizophrenia – Gender differences in schizophrenia

Introduction

Since Emil Kraepelin grouped dementia hebephrenica and paranoides under the disease concept of dementia praecox in 1896, and in 1911 Eugen Bleuler gave it a prognostically more neutral name, schizophrenia has been investigated in psychiatric epidemiology with greater persistence than has any other psychiatric disorder. However, epidemiology has contributed little to the search for the causes of schizophrenia, "a condition of obscure origin and no established aetiology" as Jablensky (1987a) recently called it. Nevertheless, the prospects for validating causal models in schizophrenia research seem to have improved.

The Morbid Risk: Stable Over Time and Populations

The main indicator of the morbid risk and thus the focus of epidemiological research on the aetiology of schizophrenia is incidence rates. Up to the present these range from a minimum of 0.08‰ (South-Verona, Italy) to 0.69‰ a year (Rochester, Md/USA) showing a marked difference between two groups of countries: the United Kingdom, Australia, and the Scandinavian countries cluster around 0.1%–0.2‰; the United States of America, Ireland and the Federal Republic of Germany around 0.3‰–0.7‰ (Häfner

1987a). Suggested explanations range from true differences in morbidity to different methods of diagnosis in the two groups of countries (see US/UK Study, Cooper et al. 1972).

The most important progress in the epidemiology of schizophrenia was made by the three schizophrenia studies coordinated by the World Health Organization (WHO 1979; Jablensky et al. 1980, 1988; Sartorius et al. 1986, 1987). By using a transnationally standardized and trained interview (PSE) that was based on an internationally agreed definition of the disease, by using computerized diagnoses at different levels of definition, and by additionally searching for untreated cases in the respective population, the "Determinants of Outcome Study" (Sartorius et al. 1986; Jablensky et al. 1988) made it possible to identify the incidence of schizophrenic disorders almost completely in ten different countries. The two essential findings are the surprising homogeneity of the syndrome of "schizophrenia" in all cultures investigated so far, and the low variation in the incidence rates when a precise, restricted definition of the disease (CATEGO S+) is used. The annual incidence rates for males and females aged 15–54 years clustered around 10/100,000 – reaching a minimum of 7/100,000 in Denmark and a maximum of 14/100,000 in the United Kingdom. The marked differences in the frequency of first onset reported in studies lacking standardized diagnostic procedures were confirmed as a tendency in the "Determinants of Outcome Study" for a broad diagnostic definition of schizophrenia (CATEGO S+, P and O) – annual rates ranging from 15 (Aarhus) to 42 per 100,000 (Chandigarh) –, and are thus accounted for mainly by different criteria of diagnosis.

In addition to the small variability of the morbid risk over countries and across cultures, the first admission rates of schizophrenia have been relatively stable over medium periods of time. In the few countries where methodologically sound studies based on national case registers were conducted, ranging over periods longer than 38 to a maximum of 130 years (Norway, Denmark, Victoria/Australia), the age-standardized first admission rates seem to have remained fairly constant (Häfner 1987a, 1988).

Is Schizophrenia Really a Disease?

So far schizophrenia seems to be almost evenly distributed over time and populations. Almost all diseases and in particular those with a homogeneous aetiology – like bacterial or viral infections, and single-gene diseases – differ considerably in their morbid risk over time and space owing to waves of spread or immunization, selection, and environmental factors. What then is schizophrenia? Is it really the only disease which is evenly distributed? "This would put schizophrenia in a class by itself and raise the question of whether it is indeed a disease?" (Zubin 1987). However, there seem to exist some other evenly distributed conditions; severe and moderately severe mental retardation, for example, tends to be evenly distributed over time and across populations in countries without major problems of malnutrition and illiteracy, as does schizophrenia (Jablensky 1986; Häfner 1987a). Mental retardation, defined by specific intelligence-test measures ($IQ \leq 60$), is the lowest section of a complex "intelligence" dimension that is normally distributed in all populations. The section of a normally distributed dimension with similar values in all populations, which is defined by the same threshold, necessarily includes a fairly consistent rate of individuals in these populations.

Could this simple model of the relative epidemiological stability of mental retardation be used for a plausible explanation of the remarkable epidemiological data on schizophrenia? Certainly not all of the model of "mental retardation" can be applied to schizophrenia. But some parallels are worth considering: first, the assumption of a continuous individual morbidity dimension, which means that between a schizophrenic psychosis and mental health there are intermediate states with a similar aetiology; secondly, the assumption that the values on this dimension are almost normally and evenly distributed in the populations, thus being comparable to the distribution of IQ values. The restrictive definition of schizophrenia, which is given with the "nuclear schizophrenia syndrome" of the PSE/CATEGO programme, would consequently be the extreme negative end of a "schizophrenia" dimension. The section would become larger and show more variability in content and size, if a broader and less precise threshold like the clinical diagnosis of schizophrenia were applied, and still larger, if symptomatic schizophrenia syndromes and spectrum disorders were included. Towards the positive end, patterns extending from mild psychiatric states to mental health would follow. If also positive or even abilities of genius are located on the same dimension, as Kretschmer (1929) had assumed and Heston (1966) and Karlsson (1984) believed they had found, has never been subject to systematic investigation.

The continuous model of schizophrenia mentioned in this context should not be confused with the assumption of a continuum of all affective and schizophrenic psychoses (Crow 1986). The revival of the old concept of *Einheitspsychose* (Neumann 1859) can be attributed to the observation that severe affective

disorders are more frequent among the close relationship of schizophrenics. If affective and schizophrenic psychoses had an aetiological dimension in common, then in the first place schizophrenic episodes could be expected to occur with marked frequency in the individual course of affective disorders, and bipolar cases among monozygotic twin partners of schizophrenics and among the offspring adopted away from schizophrenic parents. But it was found that in monozygotic twin partners of diseased patients diagnosed by applying restricted criteria (Kringlen 1987) and in children adopted away from schizophrenic parents (Kendler and Gruenberg 1984; Tienari et al. 1984) the morbidity rates for the respective other type of disorder in fact proved to be relatively small. Also, schizophrenia and paranoid syndromes rarely occur after a first episode of depression and of bipolar affective psychosis (Angst 1980; Jablensky 1987c). Thus Kringlen's statement that "... there is a moderately strong specificity in schizophrenia" (Kringlen 1987) has never been disproven.

The fact that the cumulative frequency of depressive syndromes occurring in the course of schizophrenia amounts to 70% and over may lead to the false assumption of a strong association between schizophrenic and affective disorders. This can be ascribed to the lack of aetiological specificity and to the genetic heterogeneity of unipolar depressive syndromes, which for example occur in many chronic diseases. As was assumed by Bleuler (1911), schizophrenia probably not only leads to reactive depressive conditions, but also to depression being the direct expression of the schizophrenic psychosis or of its underlying biological processes.

The Two Aspects of a Continuous Model of Schizophrenia

In principle it is conceivable that there are both a manifest psychopathological "schizophrenia" dimension and a covert disposition of gradational intensity, with and without threshold effect. In the quantitative genetics of schizophrenia, models of heritability and transmission were recently developed that start out from a single continuous variable of "liability to schizophrenia" (Baron 1987; Stassen et al. 1988). This construct includes all genetic and environmental factors determining the individual morbid risk. Theoretically, it is not dependent on the assumption of a parallel dimension of characteristic mental traits or disorders. Should "liability to schizophrenia" be linked with a threshold effect, then (comparable to an epileptic seizure) a psychotic episode could be precipitated above this threshold, whereas below it, none or no specific psychiatric disorders would be triggered in spite of a high level of stress. However, some empirical findings indicate that, in fact, psychological or psychopathological characteristics may be associated even beyond schizophrenia.

The assumption of a continuous psychopathological dimension, the extreme of which is the "schizophrenic psychosis", is not new: Kretschmer (1921) presumed a continuum extending from the "mentally sane" schizothymic character through the schizoid personality to schizophrenic psychosis. Meehl (1962) postulated the concept of a schizotaxia, schizotypy, schizophrenia dimension extending from psychosis through mild schizotypal disorders to normality. Epidemiology on the contrary has favoured the Kraepelinean single-disease model (Kraepelin 1896). The limited acceptance that models of psychopathological continuity have found so far may be explained by the fact that psychiatric practice and service planning are primarily interested in case rates, categorial diagnoses and discriminating diagnostic criteria. Discriminating criteria like Schneider's first-rank symptoms – e.g. commenting voices or delusions of being controlled by an external agency – probably create an artificial picture of distinct diagnostic categories. In fact, the majority of the characteristics of schizophrenia which proved to be invariable across cultures, such as lack of insight, suspiciousness, delusional mood, delusions or ideas of reference, delusions of persecution, and flatness of affect (Jablensky 1987a), are dimensional by nature. Theoretically they might be distributed by degrees on a schizophrenia dimension and range between psychosis, non-psychotic disorders and mental health.

Is There a Continuous "Schizophrenia-Schizothymia" Dimension?

Which findings really confirm or contradict the existence of a manifest psychopathological schizothymia dimension? The first onset of a schizophrenic psychosis is often preceded by more or less marked deficits in social competence and milder "schizophrenia-like" symptoms, for example subclinical thought and speech disorders (Meehl 1962), emotional instability etc., which in general result in reduced professional success and low rates of marriage and reproduction (Ödegard 1946, 1953, 1980; Parnas et al. 1982). However, the description of the personality traits or that of the psychiatric disorders preceding the first onset of schizophrenia does not give a homogeneous picture. Among the relatives of schizophrenic patients increased rates of psychiatric disorders are found – dependent on the degree of re-

lationship –, only part of which can be assigned to the indistinctly defined group of "schizophrenia spectrum disorders" or to the artificially defined DSM-III diagnosis of "schizotypal personality disorder". Hence, the preliminary inquiry into the individual precursor syndromes of schizophrenic psychoses and into the psychiatric disorders in the families of schizophrenic patients does not easily sustain the assumption of a fairly homogeneous schizophrenia dimension.

The fact that 68% of 142 monozygotic twin sibs of schizophrenics summarized from six systematic studies and reviewed by Kringlen (1987) differed in type and severity of psychopathology – 17% being given the diagnosis of a "possible schizophrenia", "reactive psychosis" or "borderline states", 21% showing "neurotic-like disorders", and 30% judged to be clinically normal (similar findings were reported in the adoption studies (Kety et al. 1975; Kendler and Gruenberg 1984; Tienari et al. 1984)) – supports the assumption of a considerably accumulated production of psychopathology beyond the schizophrenic psychosis by the same genotype. But at the same time the findings do not support the hypothesis of a parallel association between the genotype and a homogeneous psychopathological "schizophrenia-schizothymia" dimension.

Is There a Covert Dimension of Vulnerability to Schizophrenia and to Milder Disorders?

More consistent with the variety of psychopathological states in the "environment" of schizophrenia is the hypothesis of a partly genetically determined vulnerability that was first taken up by Zubin and Spring (1977). A continuous distribution of schizophrenia-specific degrees of vulnerability in populations would not conclusively imply an even distribution and a homogeneous psychopathology of minor psychiatric disorders associated with it. If high values of vulnerability trigger the uniform reaction pattern of the "nuclear schizophrenia syndrome", then it is quite possible that lower values might produce different psychopathological states precipitated by various environmental events, or might not at all result in abnormal behaviour patterns. Here we must consider that the vulnerability model was originally developed only for explaining the precipitation of psychotic episodes, analogous to the triggering of an epileptic attack. One would have to presume a lifelong vulnerability, which varies in extent, probably dependent on age and sex – analogous to the disposition to attacks in epilepsy – when extending this vulnerability model also to the explanation of milder states and certain personality traits in schizophrenia-prone individuals and in the familial environment of schizophrenia. Persisting traits or symptoms like social anxiety, shyness or withdrawal might either be the direct expression of a permanent and vulnerability-related hyperresponsivity or result from defence against it and from individual coping mechanisms.

Should vulnerability actually have a psychological component manifesting itself as life-long latent personality traits, then it might be experienced directly as hyper-responsivity or be deduced indirectly from repeated precipitation of episodes. This issue has not yet been given much attention. In fact, after a long course of the disease, many schizophrenics seem to experience permanently increased irritability or episodic aggravation of symptoms and relapse triggered by various events (Thurm and Häfner 1987). Under this assumption the question as to what extent learned behaviour patterns like mechanisms of external and internal control, avoidance, and inadequate coping strategies may contribute to the onset of schizophrenic symptoms and to milder reactions to increased vulnerability is of considerable interest (Strauss 1987; Nuechterlein 1987).

The question, however, if beyond this there are stable psychological indicators of a hidden, a transphenomenal vulnerability, for example appearing as deficits of cognition, attention, and perception, or as patterns of psychophysiological dysfunctions, has for quite some time been the subject of numerous studies. All psychometric and experimental findings that are fairly consistent in schizophrenics, e.g. the reaction-time cross-over phenomenon, retarded modality shift, smooth-pursuit eye movement etc., show a tendency to continuous patterns of distribution between the schizophrenic psychosis and mild psychiatric states in its familial environment. These findings thus conform with the continuous model, but they do not yet allow an external validation of the vulnerability hypothesis, since in not a single study has a sufficient specificity to a homogeneous vulnerability dimension yet been proven. It is also an open question whether cognitive and social deficits occurring in the course of schizophrenia are partly the expression of secondary changes. Course and social outcome of schizophrenia appear to be determined more by premorbid factors and later environmental influences than by characteristics of the disease in a closer sense (Biehl et al. 1986).

Pathophysiology of Psychotic Dysfunction Versus Aetiology of Schizophrenia

No less essential than the search for psychological and psychophysiological indicators of vulnerability

separate from manifest schizophrenic psychosis is the search for biological markers for the genotype or genotypes of schizophrenia which – in relation to the schizophrenic psychosis – can be assumed to show a relatively low expression rate of 0.2–0.3 (Zubin and Steinhauer 1981; Zubin 1987; Kendler 1987). It is also probable that the degree of vulnerability to schizophrenia is not only determined by genotypes, but also by environmental factors like perinatal brain damage (McNeil 1987) and family milieu (Tienari et al. 1984), by the more submissive and dependent role in a twin pair (Kringlen 1987) or by passive behaviour in the frist years of life (Parnas et al. 1982). Finally, in view of the prevalence of schizophrenic syndromes associated with various brain disorders, we must take into account the existence of phenocopies. Their proportion to the morbidity rates of schizophrenia is artificially reduced by applying exclusion criteria in the usual procedure of diagnosing.

With these facts in mind, we should consider the possibility that there may be a uniform neurobiological reaction pattern appearing as a "schizophrenic psychosis", which may be caused not only by a genetically determined specific vulnerability, but also by a variety of other causes. Possibly all the schizophrenic psychoses have in common one specific neurobiological process – like an epileptic attack – that is probably located primarily in the mesolimbic system, but is due to different underlying aetiologies. As a consequence, a multifactorial aetiology of the schizophrenic psychosis would have to be added to the assumption of a multifactorial heredity that has been frequently postulated, but not yet verified (Propping and Friedl 1987; Kendler 1987; Baron 1987). An analogue to such an explanatory model would again be that for mental retardation, since the uniform syndrome of a severe intelligence deficit is also accounted for by a variety of causes of a genetic, traumatic, infectious or toxic nature.

On the basis of the continuous model, we can partly answer the old question, why schizophrenia – and by analogy mental retardation – has not exterminated itself long ago as a consequence of its low reproduction rates and of natural selection (Hasenfuß and Magaro 1976), especially since a compensating biological advantage has not yet been demonstrated. The variety of causes and the low expression rate of schizophrenia guarantee a sufficiently large reproduction of vulnerable individuals, even if the very small group of psychotic individuals has low reproduction rates. The same is true for polygenetic modes of inheritance (Propping 1988).

With respect to the assumption of aetiological and genetic heterogeneity, we must even take into account that the schizophrenic psychosis may be one of the few ultimate and biologically uniform reaction patterns of the brain, which – by analogy with an epileptic attack or to Bonhoeffer's exogenous reaction types (Jablensky 1987b) – represents the common ultimate outcome of presumably various different pathological processes. The specific vulnerability to schizophrenia, which at high values may lead to the same psychotic pattern although there is no apparent lesion of the brain, might be only one but the most frequent causes of schizophrenia.

Testing the two versions of the continuum hypothesis is complicated by the fact that although we make use of several scales and structured interviews for assessing a very general and unspecific personality dimension of "psychoticism" (Eysenck 1952) or of "psychotic-like experiences" (Chapman and Chapman 1980) and for measuring the more defined mild thought disorder and schizotypal personalities (Andreasen 1979; Baron et al. 1981), we do not yet have sufficiently comprehensive, operationalized concepts of possible schizophrenia dimensions, standardized for field studies, nor do we have biological indicators of vulnerability that are sufficiently specific and stable over time, not to mention gene markers (Zubin 1987; Erlenmeyer-Kimling 1987). Before it would be appropriate to undertake extensive population studies on this basis, one should investigate in samples with enhanced risk the degree and the distribution patterns of the psychophysiological and neurobiological indicators found to be sufficiently stable in schizophrenia – and of symptoms and personality traits that are associated with it. Studies of this subject should be conducted in populations with different levels of genetic liability to schizophrenia, e.g. in non-affected monozygotic twin sibs, offspring of schizophrenic couples, first-degree relatives of schizophrenics. These studies would also test in a more reliable way the fitness of mathematical models for the heritability and the mode of genetic transmission of schizophrenia, which are still unknown (Baron 1987; Kendler 1987).

Is There a Contradiction Between the Even Transnational and the Uneven Socioeconomic Distribution of the Morbid Risk?

It is one of the most convincing results of epidemiological studies that the distribution of active cases of schizophrenia shows a strong socioeconomic gradient in non-egalitarian societies (Dohrenwend 1983). In this respect schizophrenia is again comparable to mental retardation in impeding social ascent. The distinctly increased prevalence in the lowest social class, in professions dying out (Ödegard 1971), and

among individuals living alone, can be partly attributed to disability as a consequence of the disease in the sense of the downward-drift hypothesis. To a smaller extent this increased prevalence may be accounted for by deficits in upward mobility prior to the first onset of the disease (Ödegard 1975; Häfner and an der Heiden 1986).

Is there a contradiction between the almost even distribution of incidence in countries and cultures and the uneven distribution within societies? No, because different characteristics of the disease may be responsible for the two levels of distribution. The almost stable distribution over time in large populations is accounted for by the accumulation of vulnerable individuals or of the underlying genotype in large populations. The rapid processes of socioeconomic mobility in open societies, partly occurring within one generation, are determined by cognitive and social competence and by mating behaviour, as far as they are influenced by the individuals themselves. In these three fields schizophrenics seem to be more frequently handicapped, even prior to the first onset of the disease, which might reduce their chances of social ascent, but not essentially influence their distribution over countries.

Two Yet Unexplained Epidemiological Findings: Birth Seasonality and Gender Differences

Two remarkable epidemiological findings have not yet been sufficiently explained: deviant birth seasonality of schizophrenics compared with that of the control populations (Boyd et al. 1986; Häfner et al. 1987), first reported by Tramer (1929), and gender difference in age at onset of schizophrenia. As to the issue of deviant birth seasonality, our own findings indicate a similar distribution pattern in the total population of mentally retarded children in Mannheim. Parallel but weaker trends were found in hospitalized mono- and bipolar affective disorders (Häfner et al. 1987; Watson et al. 1984), these probably being the most severe component of the spectrum of affective diseases, in still-births (Videbech et al. 1974), malformations of the cardiovascular system, anencephaly and diabetes mellitus, as reported by Jablensky (1987b). Most recently a group of Canadian researchers found a highly significant but opposite season-of-birth association of two temperament factors among a sample consisting of more than 2,000 school children (Maziade et al. 1988). Deviant birth seasonality is therefore unlikely to furnish a specific contribution to the aetiology of schizophrenia, which would be transmitted through conception in early summer or delivery in winter or spring, e.g. as viral infections, perinatal traumas, deficiencies in nutrition or vitamins. A more probable explanation seems to be the procreational hypothesis (Ödegard 1974; Häfner et al. 1987), which assumes that owing to an elevated genetic load a small proportion of the parents of schizophrenics and individuals with some other severe familial diseases, suffer from minor health deficits that impede their mating behaviour. An alternative explanation is based on the assumption that during pregnancy endocrine and behavior factors of the mother may be subject to seasonal influences that have an effect on the foetus and on the behaviour of the child or influence the gene expression and thereby the risk of manifestation of mendelian inherited diseases.

The subject of gender-related variation in age at first onset of schizophrenia, first mentioned by Kraepelin (1909–1915) and investigated by Braatoy as early as 1934, has been studied in recent years (Lewine 1980, 1981; Loranger 1984; Häfner 1987a). The majority of the studies have been conducted among clinical populations of schizophrenics from one or several hospitals and could not take into account sex- and age-group-related selection. When these artefacts were excluded by comparing population-based rates, as was done in some case register studies (see Angermeyer and Kühn 1988) and in a comparative study based on data from the Danish and the Mannheim case register, the gender difference in age at first admission given a diagnosis of schizophrenia under different definitions, at first admission for any diagnosis and at first ever psychiatric contact remain valid (Häfner et al.); calculated on the basis of age-group-related rates, the mean age at first admission differed between males and females by 5.4 years in Denmark and by 4.8 years in Mannheim using a wide definition and by 4.9 years in Denmark and 3.9 years in Mannheim with a restricted definition of schizophrenia.

Although age artefacts obviously do not materially contribute to the gender difference, the real age at first onset might be equal and only the time lag between the first onset of the symptoms and the first hospital admission for schizophrenia might differ between females and males. A different time lag might be the result of (a) different social roles: for example later social perception or help-seeking behaviour among females not working; (b) gender differences in symptomatology; (c) a more insidious and a less acute onset of symptoms in females; and (d) later assignment of a first diagnosis of schizophrenia to females, the last point being indirectly excluded by the findings of the study mentioned above. In agreement with the results of the "WHO Determinants of Outcome Study" (Sartorius et al. 1986; Jablensky et

al. 1988) showing a cross-culturally stable pattern of earlier mean ages at onset with males, we did not find any indication of a gender-specific time lag and of any explanation mentioned that would contribute to it.

However, gender differences in type of symptoms, age and speed of first occurrence in males and females have not yet been explored directly by applying standardized techniques in representative samples of sufficient size. How significant gender is as a determinant of symptomatology and of cognitive and social dysfunction in the course and outcome of schizophrenia, when age and duration of the disease are controlled, remains an open question.

The age difference is composed of slightly increased rates of young males falling ill prior to the age of 35 and of increased rates of elderly females with first onsets over 40. This means that an age cutoff in the diagnosis of schizophrenia – 45 years in DSM-III – does not only lower the mean age at onset to a considerable extent, but also strongly biases the sex difference itself. A similarly distorting effect can be ascribed to the criterion of time (e.g. 6 months) as to the persistence of symptoms. All these should be excluded in epidemiological studies.

The cumulative lifetime risk of schizophrenia is equal for both sexes. Males only seem to "consume" the morbid risk at a younger mean age than do females (Jablensky 1987b). This implies that so far gender effects apparently do not influence aetiology but presumably contribute to aggravating or protective factors of the vulnerability to schizophrenia. Probable explanations range from (1) psychosocial explanations – i.e. a smaller number or lower intensity of stressors combined with better coping abilities or social support at a younger age, and a larger number or more intense stressors combined with worse coping or less social support in females of advanced age compared with males – through (2) endocrine behaviour hypotheses – i.e. aggravation of risk behaviour or vulnerability by high testosterone levels in younger males and reduction of protective behaviour effects at decreasing oestrogen level in females – to (3) purely neuroendocrine hypotheses: moderation of serotonin and dopamine receptors by oestrogen or opposite effects of testosterone. The assumption of a triggering gene linked to y-chromosome does not seem probable, but is still worth testing.

Conclusions

The stability of the cumulative morbid risk over populations, medium periods of time, and sexes leads to the assumption that the schizophrenic psychosis might be the extreme on a continuous scale of psychopathological deviance or of a transphenomenal liability to the psychosis distributed normally and with almost even frequency in every populations. Those psychiatric disorders appearing before the onset of schizophrenia or found among close relatives of schizophrenics are much less uniform than is the symptomatology of the schizophrenic psychosis itself. For this reason, Kretschmer's assumption of a manifest "schizophrenia-schizothymia dimension" is less probable than Zubin's hypothesis of a covert vulnerability. Vulnerability to schizophrenia, however, should show itself by psychological or biological indicators and possibly by characteristics that can be experienced – like hyperresponsitivity to social stimuli. Different techniques for coping them might contribute to the variety of milder psychiatric disorders in the environment of schizophrenia.

The uniform syndrome of the schizophrenic psychosis unaffected by culture can presumably be understood as a preformed reaction pattern of the brain, similar to an epileptic attack or to Bonhoeffer's exogeneous reaction types. Obviously it is triggered by various causes, among which the genetically determined "endogeneous" vulnerability is presumed to furnish the largest share to the frequency of its occurrence.

There is much indication that the uniform psychopathological reaction pattern of the schizophrenic psychosis may be due to uniform biochemical or neurophysiological processes in the brain. By means of therapeutic intervention at this pathogenetic level – probably by down-regulation of the postsynaptic D_2 receptors in the mesolimbic system – the symptomatology of the psychosis can be suppressed, similar to the antiepileptic treatment of attacks. The underlying causes of the disease, understood as aetiological level, do not appear to be influenced.

Besides the pathogenetic level, at which the reaction type of a "psychosis" proceeds, and the aetiological level, at which vulnerability or the specific morbid risk is determined by genetic and environmental factors, a third level must be considered when searching for the causes of schizophrenia, namely cognitive and social deficits frequently occurring in the social course of the disease. These are mainly determined by predictors other than those of onset of psychotic episodes. Not the productive symptoms being indicators of the psychosis, but behaviour characteristics, personality traits, and environmental conditions are decisive at this level for predicting the course and outcome (Bauer-Schubart and Krum 1988).

In the future epidemiology will have to concentrate more on testing small or medium-sized models of causal associations than on collecting case rates

that are based on conventional definitions (DSM-III R or ICD no. 9). To a larger extent than has been done so far, the findings and methods of those basic sciences which correspond to the three heuristic levels of causation mentioned – behavioural sciences, neurophysiology, neurochemistry, and molecular genetics – should be included in the construction of models and their testing.

At the symposium on "Search for the Causes of Schizophrenia" held in Heidelberg in 1986, Janzarik concluded his contribution to the history of the concept of schizophrenia by stating: "There is no conclusively defined disease known as schizophrenia". Taking up this statement in discussion, Wing pointed out that schizophrenia thus began in Heidelberg (in 1896) as a disease entity and has ended here (in 1986). Even if we gave up the single-disease concept in favour of a continuous model, this would only partially be correct. As a diagnostic category, a psychosis that is defined by cut-off points on a continued scale of psychopathology, certainly continues to be a disease, now determined not taxonomically but by the location of individuals in a well-definable dimensional descriptive space (Häfner 1987b). However, schizophrenia as a "natural disease entity", first conceived by Kraepelin in 1896, in fact raises difficulties in interpreting the new epidemiological findings. Searching for the causes of schizophrenia, continuous models, as favoured by Kraepelin in his later years, indeed appear more plausible. Carpenter (1987), closing an interesting but disillusioning discussion on the very question of "What is schizophrenia?", finally stated: "I do not know – but the question how to best think about schizophrenia remains". Indeed, future research would become more promising if we organized our present knowledge to set up a valid theoretical framework and formulated productive heuristic models for testing on this basis.

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