Multicultural studies and the nature of schizophrenia: a review

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Schizophrenia, a condition of obscure origins and no established aetiology, pathogenesis and pathology, continues to be a major focus of psychiatric research and public health concern. The diagnosis of schizophrenia accounts today for well over 50% of the 'long-stay' psychiatric hospital populations in many industrialized countries, and extrapolations from the current incidence rates and demographic trends lead to predictions of further increases of the total number of cases by the end of the century, especially in Third World countries[1].

The uncertain nosological status of schizophrenia

There are few conditions in medicine that have been investigated with such persistence and with so few tangible returns over decades as has schizophrenia. Notwithstanding the current availability of pharmacological means for control of some of its florid symptoms, and in spite of the impressive advances of the modern technology for biological research, no disease marker and no laboratory test are yet available for the identification of schizophrenia, the diagnosis relying entirely on clinical judgment and convention. In practice this means that the identification of the disorder depends on the psychiatrist's interpretation of the patient's reported subjective experience, on observations of his behaviour and form of communicating, and on descriptions of the pattern in which the symptoms evolved.

The disease entity theory which underlies current diagnostic and classificatory approaches to schizophrenia is entirely inferential, drawing upon circumstantial rather than direct evidence. The arguments advanced today in support of the disease theory of schizophrenia fall roughly into four groups: (1) *genetics* (if a family history is present, the degree of an individual's genetic kinship with a person diagnosed as schizophrenic is a reliable predictor of that individual's risk of developing the condition himself); (2) *course and outcome* (in some cases schizophrenia tends to result in some degree of personality alteration which is so characteristic that it can serve as a criterion for catamnestic verification of the diagnosis); (3) *treatment response* (psychopharmacological agents, especially those acting on the brain's dopaminergic systems, can suppress many of the symptoms of schizophrenia more effectively than any other intervention); (4) *cerebral pathology* (structural brain abnormalities can be found in a certain proportion of schizophrenic patients investigated with the newer brain imaging techniques).

None of the above features is either necessary or sufficient to establish a disease status for schizophrenia. The genetic findings are compatible with different interpretations. Moreover, no family history of the disorder can be ascertained in the majority of cases of schizophrenia, and even when a genetic 'load' is undoubtedly present (as in the monozygotic co-twin of a schizophrenic or in the offspring of two schizophrenic parents) the risk of developing the disorder falls short of 50%. The treatment response is no better evidence that we are dealing with a disease entity, and the course and outcome criterion is weak as it is not evident why the same disease should not produce different outcomes, or why the same pattern of course should not occur in different diseases. The significance of the structural brain abnormalities is equally open to conflicting interpretations.

Leaving aside as extremely implausible the attempts to formulate a 'non-disease' theory of schizophrenia as a kind of social deviance or a sequel of social labelling, there are at least two alternatives to the single disease model of schizophrenia. The diathesis-stress model regards schizophrenia as a continuum of abnormal neurophysiological and behavioural responses to environmental stress in individuals possessing some kind of constitutional vulnerability. The other alternative is the view that schizophrenia is not a single disease but a collection of different syndromes or diseases, each having a characteristic clinical pattern, prognosis and cause.

Although the alternative conceptualizations of the nature of schizophrenia have very different implications for the type of research that might advance the understanding of the causes of the disorder, there is at present no decisive test to discard any of the competing theories. The essential symptoms of schizophrenia appear to be the expression of disturbances at the highest and least well understood levels of integration of specifically human neuropsychological functions – the delimitation of the self from the outer world, the encoding and decoding of information critical for social communication, and other high-order information processing for which there is no animal model to assist experimental research. Being a disorder with a relatively low incidence, onset in young adult age, and quite unpredictable evolution of the clinical manifestations over years or decades, schizophrenia is refractory even to the most powerful research strategies, such as prospective cohort investigations. Much of the costly neurobiological research is also bound to remain unproductive, unless planned and conducted in the context of a broader strategy based on a nosological construct.

Cross-cultural and epidemiological approaches

Can cross-cultural and epidemiological studies – or a cross-breed of the two approaches – provide useful guidance and testable hypotheses for clinical and laboratory research into the nature of schizophrenia?

Both the epidemiological and cross-cultural approaches to the study of schizophrenia have their birthdates around the turn of the present century.

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The origins of both were connected in one way or another with the name of Emil Kraepelin. At the instigation of Kraepelin, in 1895 Jenny Koller carried out the first community survey of psychotic disorders in two random samples of subjects in the Swiss canton of Zurich[2]. In 1904, after a trip to Java, Kraepelin published his own cross-cultural observations on dementia praecox and manic-depressive illness[3] and advocated 'comparative psychiatry' as a new approach to the understanding of the causes and mechanisms of mental disorders. He warned, however, that 'reliable comparison is, of course, only possible if we are able to draw clear distinctions between identifiable illnesses, as well as between clinical states; moreover, our clinical concepts vary so widely that for the foreseeable future such comparison is possible only if the observations are made by one and the same observer'.

Such variation of concepts and points of view could hardly be avoided at the time, and cross-cultural studies and epidemiological research took different and separate roads. Cross-cultural research and ethnopsychiatry became associated with a psychoanalytically oriented variety of cultural anthropology which principally sought evidence that psychodynamic mechanisms were cultural universals. Although psychosis was not the central concern of cultural anthropology, the conceptualizations of schizophrenia produced in its framework were sometimes original and striking. Thus to Devereux[4] schizophrenia was 'the typical ethnic psychosis of complex civilised societies', and Bateson[5] proposed the 'double-bind' hypothesis according to which a culturally determined communication conflict was at the root of schizophrenic disturbances. One of the corollaries of the ethnopsychiatric view was the expectation that the disorder would not be universally distributed and that different cultures would generate different quantities of schizophrenia.

In contrast, the epidemiological approach proceeded from a more conventional clinical definition of the disorder and attempted to measure its frequency in different societies in terms of prevalence, morbid risk and, less often, incidence. Most prevalence studies, whether based on total community surveys, population samples, or hospitalized cases, have produced similar rates ranging, with a few exceptions, from 2 to 10 per 1000 in different countries[6].

Few studies have attempted to determine the rates of manifestation of schizophrenia in sufficiently contrasting cultural groups. To mention only a few examples, Rin and Lin[7] found that although the lifetime incidence of all mental disorders among the aborigines of Taiwan (China) was the same as among the Chinese population of the island, the rate of schizophrenia in the former was significantly lower. In a study of first admissions for schizophrenia in Mauritius, Murphy and Raman[8] observed some marked differences between the three major ethnic groups on the island – the Indian Moslems, the Hindu Indians and the non-Indians – the first having the lowest and the last the highest first admission rates. In the western regions of Yugoslavia, Crocetti *et al.*[9] identified 2 geographical areas where the prevalence of schizophrenia and other psychoses was nearly 3 times as high as in the rest of the country.

The mapping of the frequency of schizophrenic disorders against cultural, ethnic and geographical variation has been slow and of limited success because of two methodological obstacles. First, comparisons of results of individual studies could not be made with confidence because of the lack of comparability of case definitions, case-finding methods and assessment techniques. Secondly, most studies focused principally on identifying and enumerating cases and, as a rule, did not provide adequate clinical data on symptomatology and course in a way that allowed secondary analysis. In the absence of such information, it is difficult to judge how similar or different were the patient populations covered by such epidemiological studies.

Schizophrenia research in the programme of the World Health Organization

The programme of collaborative clinical and epidemiological research into schizophrenia and related disorders, undertaken by the World Health Organization in the late 1960s and continuing into the present, aimed to overcome some of the methodological obstacles and clear the way for more reliable comparative investigations in different populations. The progamme involved the participation of psychiatrists and other investigators in 20 centres in 17 countries. The research strategy of the programme is characterized by the following general features:

(*a*) The use of standardized instruments for case-finding, history-taking and mental state assessment, in equivalent translations into the local languages of the populations of the study areas.
(*b*) Data collection by highly qualified psychiatrists; extensive training of the investigators in the reliable use of the instruments and monitoring of the reliability of patient assessment through joint reliability exercises and exchange of tapes or transcripts of clinical interviews.
(*c*) A two-tier diagnostic classification of the clinical information, involving a clinical diagnosis by the local team of investigators and assignment of the cases to reference diagnostic classes by a computer programme (CATEGO[10]) at the study headquarters in Geneva.
(*d*) Multiple assessments of the patients, with follow-up examinations at intervals of one, two, and five years.

The programme has included three studies (Table 1). The first (1969–1977) was the International Pilot Study of Schizophrenia[11,12], involving nine centres in Africa, Asia, Europe and North America and a total of 1202 patients aged 15–44, selected on the basis of screening criteria which required the presence of psychotic symptoms and excluded gross cerebral pathology, chronic psychotic conditions of long duration, sensory defects and mental retardation. The majority of the patients (811) had a clinical diagnosis of schizophrenia and the remaining 391, selected for comparison purposes, had diagnoses of affective or reactive psychoses, neuroses and personality disorders. Each patient had a detailed standardized clinical examination at the point of inclusion and a complete standardized reassessment two years and five years later (82% of the initial cohort had a two-year follow up and 75% had a five-year follow up).

The second WHO study was designed to explore more closely the manifestations and course of behavioural impairments and social disability in schizophrenic patients of recent onset. It included 520 patients in seven countries who were examined initially and also at one-year and two-year follow-up assessments (one of the centres carried out periodic re-examinations every six months, and two centres undertook further re-assessment at five years). In

Table 1. The WHO programme of cross-cultural research in schizophrenia (1967-85)

	International Pilot Study of Schizophrenia (IPSS)	*WHO collaborative study on psychiatric disability*	*Determinants of outcome of severe mental disorders*
Number of centres	9	7	12
Countries	China (Taipei), Colombia, Czechoslovakia, Denmark, India, Nigeria, UK, USA, USSR	Bulgaria, Federal Republic of Germany, Netherlands, Sudan, Switzerland, Turkey, Yugoslavia	Colombia, Czechoslovakia, Denmark, India, Ireland, Japan, Nigeria, UK, USA, USSR
Number of patients	1202	520	1379
Main areas assessed	Mental state (PSE), past history, social description, course and outcome	Mental state (PSE), past history, sociodemographic description, disability in social roles, behavioural impairments, pattern of course	Mental state (PSE), past history, course and outcome, disability in social roles, stressful life events, expressed emotion, perception of illness, family functioning
Diagnosis	Clinical (ICD-8), computer (CATEGO), statistical clusters	Clinical (ICD-9), computer (CATEGO)	Clinical (ICD-9), computer (CATEGO), DSM-III (some centres)
Follow up	2 years, 5 years	1 year, 2 years, 5 years	1 year, 2 years

addition to the Present State Examination (PSE)[10], which was used as a standard mental state interview throughout the WHO programme, two new instruments were developed especially for this study. One of them was the Psychological Impairment Rating Scales (PIRS), designed to describe communication and social skills deficits in everyday behaviour (many of these disturbances could also be seen as 'negative' symptoms of schizophrenia). The other instrument, the WHO Disability Assessment Schedule (DAS), served to elicit and rate information on social role performance and the environmental factors that might influence it[13].

The third and most recent study (1978–1984), Determinants of Outcome of Severe Mental Disorders, had a more complex design and included a total of 1379 patients assessed at 12 research centres in 10 countries. The core of the project was an epidemiological case-finding and clinical study which aimed to provide data on the comparative incidence of schizophrenic disorders in different geographical areas, the frequency of various patterns of course, and the relationship between epidemiological measures and alternative diagnostic classifications of the cases[14]. It involved a continuous 2-year surveillance of psychiatric and other medical services, social agencies, and alternative sources of care such as traditional or religious healers, in defined catchment areas. The case-finding method involved an active search for individuals making first lifetime contacts with such facilities because of manifest or possible psychotic illness. A screening procedure was applied to identify subjects with probable schizophrenic or other non-affective illness, and it was followed by a full mental state, history and diagnostic assessment of the eligible cases. Follow-up examinations were carried out one year and two years after the initial screening. The cohorts collected in this manner were considered to approximate a representative incidence sample. The great majority of the patients (86%) were identified within the first 12 months of the onset of the disorder and practically all patients were included in the study within 3 months of their first contact with any service – i.e. before treatment effects or social factors could pathoplastically alter the manifestations and course of the illness. In addition to the standard clinical, social and diagnostic assessment, subgroups of the patients participated in special investigations, such as an exploration of life events preceding the onset of symptoms[15], a study of the effect of expressed emotion in a relative on the probability of relapse[16], a study of the perception of the patient's behaviour by the social environment, and an investigation of the rate of development of various social role dysfunctions.

Results of the WHO studies

The main findings of the WHO multi-centre programme can be summarized as follows:

(*1*) The major psychopathological syndromes defining the clinical entity of schizophrenia since its delimitation by Kraepelin[17] and Bleuler[18] have been found to occur in all the populations and geographical areas covered by the WHO investigations. Although no single symptom was invariably present in every patient and in every setting, the clinical pictures associated with a diagnosis of schizophrenia were remarkably similar at the level of symptom profiles (Table 2). Patients diagnosed as schizophrenic tended to have high scores on lack of insight, suspiciousness, delusional mood, delusions or ideas of reference and persecution, flatness of affect, auditory hallucinations, and the delusion of being controlled by an external agency.

The application of CATEGO demonstrated a high degree of agreement between the centre diagnosis and the computer classification of the cases (an average of 87% in the IPSS and between 63% and 95% of the cases in the different centres in the Outcome Study). Varying proportions (between 31% and 85%, an average of 56%) of the patients meeting the general criteria of a non-affective functional psychosis and diagnosed by clinicians as schizophrenic also exhibited one or more of the 'first-rank' symptoms considered by Schneider[19] as reliably distinguishing schizophrenia from other non-organic psychotic illnesses. These symptoms appeared to define a subpopulation of schizophrenic patients characterized by a generally high frequency and intensity of 'positive' psychotic symptoms which manifested great similarity across the cultures.

(*2*) Against a background of overall similarity in

Table 2. International Pilot Study of Schizophrenia (IPSS). Ten most frequently positive 'units of analysis' in patients with diagnosis of paranoid schizophrenia in Aarhus, Agra, Cali, Ibadan, London, Moscow, Prague, Taipei and Washington

1) Lack of insight	55% (Was)	100% (Agr, Mos)
2) Suspiciousness	67% (Pra)	93% (Agr)
3) Delusions of persecution	60% (Cal)	93% (Agr)
4) Delusions of reference	54% (Mos)	73% (Agr)
5) Ideas of reference	46% (Aar)	86% (Tai)
6) Uncooperativeness	28% (Lon)	82% (Aar)
7) Inadequate description	32% (Lon)	83% (Was)
8) Delusional mood	36% (Pra)	75% (Cal)
9) Flatness of affect	41% (Iba)	68% (Lon)
10) Auditory hallucinations	31% (Was)	64% (Pra)

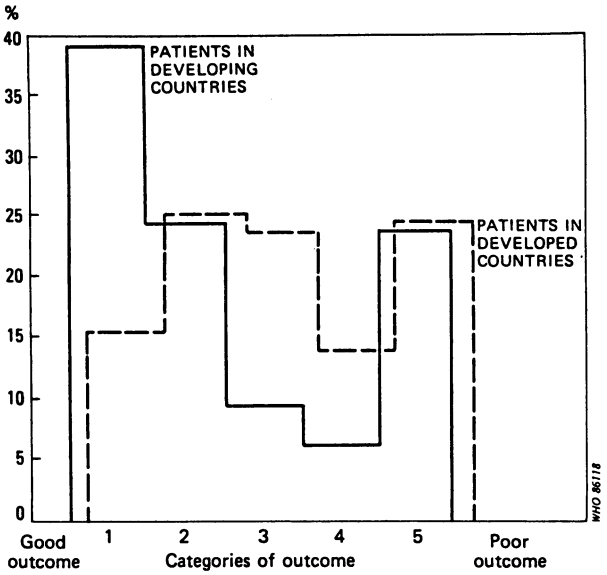

Figure 1. Distribution of 233 followed-up schizophrenic patients in developing countries and 295 followed-up schizophrenic patients in developed countries over 5 categories of 2-year overall outcome. (Reproduced from Sartorius et al.[20], *with kind permission)*

the presentation of schizophrenic illnesses in different cultures, there were differences among the individual centres and, in particular, between the study areas in developing countries and in industrialized countries. Such differences are of interest because they may reflect pathoplastic effects of culture rather than chance variation. First, a significantly greater proportion of patients in the developing countries who met the symptomatological criteria for schizophrenia had an acute onset of the disorder. Secondly, patients in developing countries exhibited fewer affective symptoms (e.g. depression) as part of the initial manifestations of schizophrenic illnesses than their counterparts in European, North American and Japanese centres. Thirdly, patients in developing countries had higher scores on auditory and visual hallucinations. However, these features of the presentation of psychotic illnesses in developing countries did not cluster together as a separate syndrome, different from the 'central' schizophrenic syndrome. On the contrary, they were present in association with the 'nuclear' syndrome defined by Schneiderian first-rank symptoms.

(*3*) One of the striking findings of the follow-up phase of the IPSS was the contrast between the initial symptomatological similarity of the schizophrenic patients both within and across centres, and the great variety of forms of course and outcome which their illnesses took over the subsequent five years. Generally, there were three characteristic types of course. A proportion of the patients had a single acute or subacute psychotic episode which was followed by a complete recovery without further attacks. At the other extreme were the patients who remained ill throughout the follow-up period and had chronic psychotic symptoms and severe social incapacitation. An intermediate group comprised patients who had several psychotic attacks with interposed remissions which could be complete or partial. In the IPSS study population, 27% of the schizophrenic patients fell into the first group, 26% into the second, and 47% into the third. However, the frequency of the three patterns of course varied significantly among the centres. While 58% of the Nigerian patients and 51% of the Indian patients had a single psychotic episode followed by a complete remission, the corresponding percentages for this type of course in the remaining centres range between 6% in Denmark and 27% in China (Taipei). In contrast, 50% of the patients in Denmark, 47% in the USA, and 30% in the UK and Czeckoslovakia had a chronic unremitting psychotic illness, compared with only 7% in Nigeria and 20% in India. An index of 'overall outcome', combining the score on pattern of course, the summary duration of psychotic episodes, and the scores on quality of remissions and degree of social impairment, demonstrated that the IPSS patients in the developing countries had a significantly better outcome than the patients in the developed countries (Figure 1).

A number of predictors associated with each of the three patterns of course were identified by multivariate statistical analysis. The remitting type was predicted by an acute onset, absence of previous episodes of psychiatric illness, and stable family background. The chronic pattern represented usually the extension of an illness which had started insidiously in the past, in a socially withdrawn person with a long history of abnormal behaviour who was also likely to be single, divorced, separated from spouse, or widowed. The periodic recurrent pattern was more frequent in females and the initial episodes of the illness were characterized by an admixture of schizophrenic, affective and neurotic symptoms.

While none of these predictors would be unexpected to clinicians, the three different patterns of course correlated poorly with the initial diagnostic classification of the cases. Neither the ICD subtypes of schizophrenia, nor the CATEGO classification of 'nuclear' and non-'nuclear' schizophrenic syndromes predicted adequately the subsequent pattern of course, with the exception of the distinction between a subgroup combining simple and hebephrenic schizophrenia and the subgroup of cases diagnosed as schizoaffective.

This finding underscores the difficulty of reconciling the two main approaches to the diagnosis of schizophrenia – one emphasizing primarily course and outcome, and the other giving priority to the cross-section of psychopathological manifestations.

Although the existence, within the IPSS population, of a subgroup of patients with acute transient psychotic illnesses which bear no intrinsic relationship to schizophrenia but mimic some of its symptoms, cannot be excluded, the data support the notion of a pathoplastic effect of the social and cultural environment on the course of schizophrenic disorders.

(*4*) The incidence rates of schizophrenia, measured in terms of annual rate of first lifetime contacts with any type of service, are comparable in culturally distant populations and vary by only a factor of three between areas with high rates (e.g. a rural area near Chandigarh, India) and areas with low rates (the county of Aarhus, Denmark). Although the differences observed among the six centres in the Outcome Study which achieved a fairly complete coverage of all first contacts were statistically significant ($P<0.05$), their magnitude was not of an order that would suggest major cultural contrasts in the incidence of schizophrenia. Even more importantly, the application to the data of a restrictive diagnostic criterion (the CATEGO class S+ defining a 'central' schizophrenic subgroup) resulted not only in lower incidence rates as expected but also in a marked reduction of the inter-area variation of the rates (Figure 2). This was contrary to the prediction that, as the mean rate of occurrence of a disease declines, the spread of the individual rates for the different centres would increase (because the chance addition or omission of a single case would result in a greater percentage difference in the smaller sample). It could be inferred, therefore, that the 'nuclear' schizophrenic syndrome may indeed be occurring at an almost uniform rate in different populations.

This inference was further supported by the non-random distribution of the age at onset and the marked differences in this respect between males and females (in the absence of sex differences in the overall incidence rates when the entire age range 15–54 was considered). In virtually all centres, the illness onsets in males showed a peak in the age groups younger than 24, while in females the onsets tended to cluster in older age groups. With the application of the stricter CATEGO S+ criterion these distinctions became even sharper.

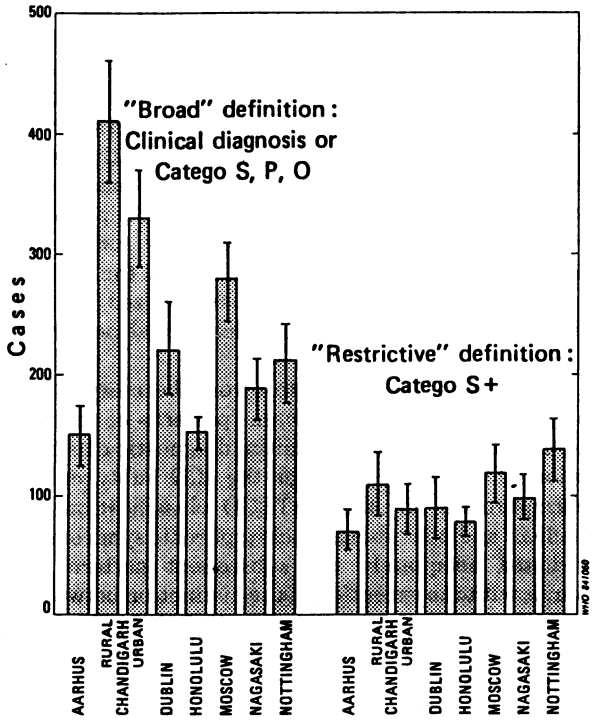

Figure 2. Incidence rates per millon population age 15–54 (both sexes): for the 'broad' and for the 'restrictive definition of schizophrenia. (Reproduced from Sartorius et al.[14]*, with kind permission)*

Implications of the WHO data for conjectures about the nature of schizophrenia

The selected findings of the WHO research programme presented here are still of a preliminary nature. Data analyses now in progress may add important new material, although it is unlikely that the essential configuration of the results will be changed. With this assumption, it may be tempting to reflect on the possible implication of the findings for the general disease theory of schizophrenia.

A first corollary of the findings is that any extreme position of cultural relativism as regards the identification of schizophrenia in different populations would be untenable. The fact that a specific pattern of symptoms can be identified reliably in widely varying cultural settings, and that this pattern corresponds fairly well to a generally accepted clinical description of the schizophrenic syndrome, is only one of the findings that has to be accounted by the relativist position. Another is the clear-cut symptomatological distinction, observed in all settings, between conditions diagnosed as schizophrenic and those of other types, e.g. manic-depressive illness. A third observation is the similarity of certain characteristic manifestations of schizophrenia across different cultures. Considering the variety of social norms, beliefs, attitudes and techniques for coping with stress which exist in different cultures, the similarity of the subjective experience of certain schizophrenic symptoms is quite striking. For example, some of the 'first-rank' symptoms refer to highly specific intrapsychic phenomena which could serve as a 'marker' for the identification of the 'nuclear' schizophrenic syndromes. It is difficult to think of a common 'cultural' reason for acutely disturbed subjects in different cultures to experience hallucinatory voices discussing them precisely in the third person or commenting on their every action and thought; feel their thoughts being stopped, taken away, 'read' by some alien agency, or 'broadcast' at large. Yet this is what patients in cultures as different from one another as Denmark and Nigeria describe, using almost identical words or phrases. Unless this observation is shown to be an artefact of the interviewing technique – which is unlikely – it suggests strongly that the forms of schizophrenic experience, i.e. the specific disorders of perception, thought, self-image and ideation, have a common pathophysiological basis and are universal.

A second corollary is that the finding of similar incidence rates of the schizophrenic syndrome in different populations need not necessarily imply that the causes of schizophrenia are exclusively 'biological'. Considering the marked genetic, constitutional, nutritional, and other biological differences among the populations studied, the emergence of similar rates of any complex disorder would be expected. Insofar as a methodological bias in case-finding and ascertainment can be excluded, schizophrenia appears to behave differently from other multifactorial diseases like diabetes or ischaemic heart disease, which show enormous variations in incidence

in the same populations. If schizophrenia is not a single disease of uniform aetiology and pathology, but rather a broadly defined syndrome that may arise as a response to a variety of pathological processes or developmental anomalies – some of them with strong genetic contribution and some the result of environmental factors – then the comparable rates of manifestation could be seen as the expression of a similarly distributed liability for a 'schizophrenic' type of response rather than as a reflection of a similar distribution of identical primary causes. A possible analogy may be found in epilepsy, which seems to be one of the few other disorders occurring with similar rates in very different populations, the ictal discharge being a response modality of a certain neurophysiological organization which can be activated by a variety of lesions and stimuli.

A third corollary is that research into the conditions which may facilitate or inhibit the manifestation of a schizophrenic syndrome or 'reaction type' may be a fruitful approach. It is well known that schizophrenic symptoms do arise in association with central nervous system intoxications (e.g. LSD, PCP, amphetamine), temporal lobe epilepsy, and a variety of cerebral degenerative diseases, but little is known about the determinants of individual susceptibility to schizophreniform illness in some cases, to acute confusional episodes in other cases, and to cognitive disorders of a dementing type in yet another proportion of subjects. Even less is known about the psychosocial and cultural conditions that may either preclude or augment the probability of a schizophrenic response to pathological lesions. The WHO studies have only pointed to a possibility that in technologically less complex cultures the chronic deteriorating forms of schizophrenia may be less frequent than in societies imposing upon their members complex, conflicting and potentially disorienting cognitive requirements. Knowledge about the occurrence of schizophrenia in radically different societies – e.g. in pre-literate cultures or hunter-gatherer groups – is lacking and extremely difficult to obtain. The possibility, however, cannot be excluded that the application of the modern research technology in such explorations may bring us closer to a new vantage point from which to investigate the elusive nature of schizophrenia.

This may involve the questioning of certain basic assumptions, an example of which was provided by Kraepelin who, towards the end of his career[21], put the problem of schizophrenia into a perspective which was fundamentally different from his own earlier view. In his article '*Die Erscheinungsformen des Irreseins*' he proposed that:

'the affective and schizophrenic forms of mental disorder do not represent the expression of particular pathological processes, but rather indicate the areas of our personality in which these processes unfold ... It must remain an open question whether this is due to general human psychological mechanisms operating in combination with pathological changes, or whether hereditary factors make certain areas more susceptible and accessible to pathological stimuli ... The various syndromes of illness may be compared with the different registers of an organ, any of which may be brought into play according to the severity and extent of the pathological changes involved. They impart a characteristic tone to the illness quite irrespective of the mechanism which has brought them into play ... Schizophrenic symptoms are by no means limited to dementia praecox. We find them also in varying degree in many morbid processes in which there is widespread destruction of nerve tissue ... There is no doubt, however, that schizophrenic symptoms may also occur without any damage to cerebral tissue'.

Sixty-five years later, we find ourselves challenged to define a better research agenda for biological and epidemiological psychiatry.

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