Chapter 5 Discussion of the findings and conclusions

In spite of nearly a century of research, the epidemiology of schizophrenia still contains many uncharted or poorly explored areas. First, the possible existence of differential rates of occurrence of the disorder in various age groups and sexes in populations geographically and culturally apart, has been a matter of considerable interest (Murphy, 1978; Torrey, 1980). However, until the present time only fragmentary empirical data have been available on this issue, and the different views expressed resort more often to speculation rather than to an epidemiological data base.

Secondly, few clinical studies have been based on representative samples of cases in early stages of the illness, before its symptoms and course have been modified by treatment and, very likely, by social attitudes. This has hampered research on the 'natural history' of schizophrenia, which continues to be viewed by many as a process invariably leading to some degree of deterioration and disablement. Prognostic indicators that could be used early in the course of the illness have usually been sought on relatively small and unrepresentative patient samples, and often without appropriate data collection instruments and statistical models.

Thirdly, widely diverging views continue to be held on the scope and boundaries of the diagnostic concept, as well as on the extent to which a diagnosis of schizophrenia made in one setting, or by one 'school' of psychiatry, can be meaningfully replicated in another setting, or by another 'school'.

These issues are basic to the very notion of schizophrenia as a specific psychopathological condition. It has been pointed out (Shepherd, 1982) that progress in the search for aetiological factors, pathogenic mechanisms, and disease markers can be seriously impeded unless the essential parameters of its incidence, cross-culturally constant clinical manifestations, and pattern of course are laid down with sufficient clarity.

THE STRATEGY OF MULTI-CENTRE COLLABORATIVE RESEARCH

In the instance of a condition of a relatively low population incidence, such as schizophrenia, the multi-centre collaborative research has advantages over single centre studies and is more likely to significantly increase epidemiological and clinical knowledge. Large numbers of cases can be accumulated in less time, and the individual patient samples, identified in different areas, provide opportunities for multiple replications of the search for 'robust' characteristics of the disorder that show constancy and repeatability in the face of cultural variation and other, demographic, ecological and biological differences between populations.

Such multi-centre collaborative research has been the hallmark of the mental health programme of the World Health Organization in the past two decades, and the present project on Determinants of Outcome of Severe Mental Disorders is part of a series of cross-cultural investigations which up to date have involved teams of investigators in over 40 countries. Together with the International Pilot Study of Schizophrenia – IPSS (1202 patients in nine countries – WHO, 1973, 1979); the Study on Psychiatric Impairments and Disabilities (520 patients in seven countries – Jablensky *et al.* 1980); the Study on Depressive Disorders in Different Cultures (570 patients in four countries – Sartorius *et al.* 1983); and a recent multi-centre investigation of acute transient psychoses (to be published), the Outcome study is a component of a collaborative programme which possesses several features that are rarely encountered together. These features are as follows:

(i) multi-centre and multi-cultural setting in which field work is carried out by research workers belonging to the same culture as the subjects;

(ii) use of uniform and standardized research instruments and techniques which make possible

comparisons between patient samples in different settings;

(iii) prospective observation, including multiple follow-up examinations of patients and key informants;

(iv) assessment of patients by highly skilled clinicians, rather than by lay interviewers or research assistants.

In addition to these features, the Outcome study employed an epidemiological approach to case finding based on symptoms, which represents a considerable extension of, and improvement over, the first admission-by-diagnosis method, used previously in investigations of the incidence of schizophrenia.

Conceptually, the Outcome project reflects aspects of the 'state of the art' in schizophrenia research in the mid-1970s, when new trends like the experimentation with 'operational' diagnostic criteria, and their application to studies of the major mental disorders, were gaining ground. A number of studies, initiated around the same time, have taken different methodological approaches. While none of these studies (the Outcome project included) have yet provided conclusive answers to the unresolved questions about the nature of schizophrenia, it will be important, as results are being published, to assess carefully whether the understanding of schizophrenia can be significantly furthered by epidemiological and clinical means, or a major breakthrough ought to be first awaited in the domain of biological research before any new large-scale epidemiological study is undertaken.

Having reviewed the principal methods and results of the 'core' study of the Outcome project in the preceding chapters, it is now important to examine their significance and possible interpretation in relation to several questions resulting from the statement made in the opening paragraphs above.

1. In what sense can it be said that the patient population assessed in the present study is 'representative' of the universe of disorders that would broadly be classified as schizophrenic according to internationally accepted criteria? In this context, it would be especially important to compare the Outcome study patient samples with the IPSS series of patients.

2. How effective are the psychopathological and diagnostic criteria employed in the present study as tools for dividing the disorders broadly grouped as schizophrenic into groups and subtypes with distinctive symptomatological and other associated features which could provide useful leads for further, aetiologically orientated research?

3. What new knowledge has been collected in the present study on the course and outcome of schizophrenic disorders and on their determinants?

4. What are the implications of the findings reported here on the incidence of schizophrenia in different geographical areas?

A COMPARISON BETWEEN THE OUTCOME STUDY AND THE IPSS: THE ISSUE OF REPRESENTATIVENESS

A review of epidemiological, including follow-up, studies on schizophrenia in the 1960s and early 1970s (WHO, 1979) concluded that methodological problems, especially lack of standardization of diagnostic criteria and outcome criteria, limited seriously the comparability of results reported by different research workers and in different cultures. Nevertheless, it was pointed out that 'despite improvements in social, psychopharmacological and other treatments of schizophrenia, no matter how narrowly or broadly schizophrenia is defined, this disorder still has the potential to develop into a chronic disorder'.

This conclusion, based on a selective review of about a dozen major studies published between 1939 and 1972, had to be modified in the light of the results of the two-year follow-up of IPSS patients, which demonstrated that, 'at least as far as short-term course is concerned, symptomatologically similar schizophrenic patients may differ greatly with regard to course and outcome' (WHO, 1979). One of the striking findings of the IPSS was the marked tendency for schizophrenic patients in developing countries to have less severe course and outcome than patients with comparable initial clinical pictures in the developed countries.

The IPSS findings were underscored by the results of several other studies, published subsequently. Although based on methods and design often quite different from those of the WHO study, they reported high proportions of favourable outcomes not only for patients diagnosed as schizophrenic in traditional cul-

tures (Waxler, 1979), but also for European patients, followed up over years, and, in some of these studies, over decades (Bleuler, 1972; Ciompi, 1980; Gross *et al.* 1981). In the report on a 5-year prospective investigation of 121 patients, Watt *et al.* (1983) pointed out that little attention had been paid in previous studies to the representativeness of patient groups, and described the manner in which their own patients were selected with a view to obtaining a representative group of schizophrenics. This study used assessment methods and criteria comparable to those of the IPSS, and its findings showed a good outcome in nearly 50% of the cases. However, only one-third of the patients were first admissions, and although the sample could be considered a representative cross-section of the schizophrenic population under treatment, it was not an incidence cohort.

The problem of representativeness is central to research into the clinical spectrum and 'natural history' of the conditions diagnosed as schizophrenic. It implies the identification of all cases (or a representative sample of them) who meet specified criteria for the disorder and are members of a defined population. If selection criteria restrict admission to the study only to patients with clearly established symptoms and signs of schizophrenia as stipulated by many of the current 'operational' criteria (Fenton *et al.* 1981), it is likely that the sample would consist predominantly of patients with severe illnesses, many of them chronic, and with a history of previous treatment. Such a sample would be perfectly adequate for assessing the effects of a given treatment, but it is unlikely to advance research into risk factors and mechanisms underlying the course of the disorder. It would not include, for example, the less severe and less 'typical' forms which are a natural part of the clinical spectrum of any disorder (not only schizophrenia), and it would miss the early stages of illness, which may be important for the prediction of its subsequent evolution.

The present study was designed with a view to making some advance over the IPSS in regard of these aspects of representativeness of the patient population. As pointed out in chapter 1, the aim of the case-finding strategy chosen was to collect a series of patients at a point as close as possible to the onset of their illnesses, and in a stage when their clinical presentation and social functioning would not have been affected by treatment or by the institutionalized roles that are frequently imposed on schizophrenics and their families by the environment. The findings suggest that, by and large, this aim has been achieved and that the study has been successful, probably for the first time on such a scale, in collecting a sample of practically untreated patients of recent onset.

A comparison with the IPSS shows that 40% of the patients with a diagnosis of schizophrenia in that study had had previous attacks and treatment; all the patients in the present study were included during the first episode of psychotic illness, and 86% entered the study within less than a year after the onset of symptoms. While in the IPSS the episode of inclusion had lasted six or more months before the initial assessment in 34% of the cases, the corresponding figure for the Outcome study is 20%. The proportion of IPSS schizophrenic patients with sudden onset of the episode was 12%; using somewhat different criteria, this proportion was found to be 36% in the present study.

All these findings show that, in accordance with the research aims, the Outcome study sample is characterized by less chronicity, shorter previous history of illness, and less exposure to psychiatric services. At the same time, a number of the sociodemographic characteristics of the two samples are quite similar. Although the IPSS included patients within the age groups 15 to 44, the male to female ratios of the schizophrenic patients in the two samples are comparable (see Table 5.1).

Table 5.1. *Male to female ratios of schizophrenic patients in the IPSS and Outcome study groups*

Age group	IPSS	Outcome study
15–24	1·3	1·6
25–34	1·2	1·2
35–44	0·6	0·7
All ages	1·0	1·2

The percentage of single, divorced or separated patients in the Outcome study is slightly higher (63%) than in the IPSS (59%) but the proportions of patients living alone is the same (9%). Ten per cent of the IPSS patients, and 12% of the Outcome study patients, were

illiterate and never went to school. The proportion of schizophrenic patients who had never been employed was 21% in the IPSS and 24% in the Outcome study. Exactly the same proportions (26%) of the IPSS schizophrenics and of the Outcome study patients (26%) had at least one relative with mental illness, although the method of data collection in the latter study was considerably more elaborate.

Another aspect of the problem of representativeness is related to the question whether the sample of patients in the Outcome study is comprehensive, as regards inclusion of all the varieties of the schizophrenic syndrome, and specific, in the sense of not being diluted with conditions which on closer scrutiny would not satisfy even broad criteria for a diagnosis of schizophrenia.

In the absence of external validating criteria, schizophrenia remains a clinical concept, and the sampling of cases cannot be guided by anything better than a carefully evaluated knowledge base, shared by the greatest possible number of investigators. This was the assumption which led to the adoption of a dual criterion for inclusion in the present study: the simultaneous use of the clinical diagnosis of the investigators and of the CATEGO computer classification of psychopathological syndromes. The 'outer' boundary of the disorders qualifying as schizophrenia or schizophrenia-related was defined by either: (i) the clinical diagnosis of schizophrenia or one of the several ICD-9 categories phenomenologically close to it; or (ii) the S, P and O CATEGO classes, in instances where the clinical diagnosis might prove too restrictive. The CATEGO S+ class, defined by the presence of Schneider's first-rank symptoms, was used as an index defining a 'core' of cases less likely to evoke disagreement as to their nosological status than the broader definition. Compared to the IPSS, this procedure was intended to be both more flexible, by giving more room to clinical judgement in doubtful cases, and more specific, by providing operationally defined levels of diagnostic classification.

Although it is difficult to draw strict parallels between the IPSS and the Outcome study with regard to the symptomatology and diagnostic class distribution of the patient samples (because of the use of different editions of the PSE and slightly different CATEGO versions), some gross differences and similarities stand out. At the level of diagnosis assigned by the field research centres, the ratios of schizophrenia, paranoid states, and reactive paranoid psychoses were very similar in the two study samples – 91:3:6 in the IPSS and 92:3:5 in the Outcome study. However, there were differences in the distribution on individual diagnostic subtypes. Paranoid schizophrenia (ICD 295.3) was more frequent in the IPSS sample (40% of all cases) than in the present study (29%). Schizoaffective disorder accounted for 13% of all diagnoses of schizophrenic patients in the IPSS, but for less than 6% of the Outcome study diagnoses. The largest difference concerns the frequency of the diagnosis of acute schizophrenic episode – over 23% in the present study and less than 10% in the IPSS. The difference is probably a reflection of the case finding strategy of the Outcome study because it correlates with the recency of onset in a substantial proportion of the patients.

As regards symptomatology, comparison between the two studies can be made on the basis of the major CATEGO classes assigned to different subgroups of patients. This, of course, is meaningful only for the centres which participated in both studies: Aarhus, Agra, Cali, Ibadan, Moscow, and Prague. Table 5.2 shows the percentages of IPSS and Outcome study patients with centre diagnosis of schizophrenia, paranoid states, or psychogenic paranoid psychosis, who were assigned to CATEGO classes S, P and O. While in four of these centres the rates of concordance in the two studies are very similar, there was some decrease of the concordance rate in Aarhus, and an increase in Moscow. Changes in the diagnostic habits may have taken place in the centres over the years that separate the two studies, but it is more likely that the differences, as regards Aarhus are closely related to the nature of the sample, and in the case of Moscow, to the earlier timing of the PSE assessment after inclusion of the patients in the present study. Many of the Aarhus IPSS schizophrenics had a longer history of previous illness than the patients in the other IPSS centres. This was not the case in the present study, and it is therefore not surprising that the rate of CATEGO S, P, O would be lower. The greater concordance between clinical diagnosis and CATEGO class in the Outcome study

Table 5.2. *Comparison of diagnostic concordance rates between the International Pilot Study of Schizophrenia (IPSS) and the present study (only centres which took part in both investigations)*

		Aar	Agr	Cal	Iba	Mos	Pra
Percentage patients with centre clinical diagnosis ICD 295, 297 or 298.3–9 who have been assigned CATEGO classes S, P or O	IPSS	95	91	88	96	63	83
	Outcome study	78	92	94	95	79	92

sample in Moscow may be due to the fact that in the present study the patients were administered the PSE early after intake, i.e. at the height of florid symptoms, while in the IPSS such assessments often took place somewhat later, often after a period of treatment, when the intensity of symptoms had abated. These comparisons strengthen retrospectively the case for considering the IPSS series of schizophrenic patients also to be a representative selection of cases, in spite of the less rigorous nature of the inclusion procedure from an epidemiological point of view.

VALIDITY OF THE DIAGNOSTIC CLASSIFICATION OF THE CASES

Assuming that a representative sample, reflecting a wide clinical horizon of non-affective psychotic disorders, has been obtained in the Outcome study, the first question that arises is: in what sense can the disorders investigated in the Outcome study be regarded as 'schizophrenic'?

It is well known that 'schools' and traditions in psychiatry, across and within countries, differ with regard to the conceptual definition of schizophrenia and the criteria thought to be of importance in establishing the diagnosis (Berner *et al.* 1983). Different theoretical positions on these issues are also represented within the network of research centres which took part in the present study. However, a critical review of the existing variation in the approaches to the taxonomy of schizophrenia (WHO, 1981) nevertheless concluded that 'schizophrenia is a valid and useful concept, defining a disorder or groups of disorders of world-wide occurrence for which a predisposition is genetically transmitted'.

The extent to which diagnostic variation can actually invalidate the assessment of epidemiological data on schizophrenia is not precisely known. Considering the remarkable stability of prevalence rates of schizophrenia, reported from different parts of Europe where various psychiatric 'schools' have been competing for decades, one is inclined to think that the effects of such diagnostic variation need not be exaggerated. The differences between the various 'schools' and approaches usually concern the margins of the diagnostic concept, but not its core; therefore they are likely to affect the estimates of the upper limits of the range of morbidity indices, but would have less effect on its lower limits.

The study presented here took an explicitly empirical and pragmatic approach to the diagnostic definition of 'caseness'. Instead of taking as its point of departure any one particular concept of schizophrenia, the first step of case definition at the screening stage consisted in the ascertainment of symptoms and signs which most psychiatrists would describe as either psychotic or strongly suggestive of psychosis, and which were unlikely to be a manifestation of an underlying affective disturbance. Since gross brain damage was also excluded at that stage, these criteria restrict the universe of 'caseness' to an area that might be subdivided and labelled differently, but is certain to contain most of the symptoms and syndromes which would be regarded as schizophrenic by any 'school'. The results of the second stage, at which diagnostic classification was carried out after a standardized clinical assessment, confirm the advantage of starting the case finding with an enquiry about symptoms and signs rather than about diagnoses: in the eight areas for which incidence rates are reported, a total of 80 cases would not have entered the study if case finding had been based only on a clinical diagnosis. All of these 80 cases, which met the screening criteria but were given centre diagnoses other than schizophrenia and schizophrenia-related disorders, were classified by the CATEGO program into one of the 'schizophrenic' classes S, P, or O, and were symptomatologically similar to the patients who were assigned to the same CATEGO classes but had a centre diagnosis of schizophrenia.

The high rate of concordance between the ICD diagnostic inclusion criteria and a CATEGO classification as S, P, or O (no less than 80% in seven of the study areas and 64% in one area) is an indication of the valid inclusion of the large majority of cases. Both in the IPSS (WHO, 1973) and in other studies (Scharfetter *et al.* 1976; Brockington *et al.* 1978; Lewine *et al.* 1982), membership in the 'broad' S, P, O group has been shown to correlate highly with clinical consensus on a diagnosis of schizophrenia. Since, however, the reverse is not necessarily true (i.e. not all CATEGO-discrepant cases with a clinical diagnosis of schizophrenia in one setting would be diagnosed as schizophrenia in another setting), it was considered important to calculate not one but several rates of incidence for each area, and to include the marginal cases in the 'broad' definition, but not in the other three definitions, which require S, P, O membership.

Assuming that a representative sample, reflecting a broad clinical agreement on the scope of schizophrenia and related conditions has been obtained in the Outcome study, the next question concerns the further diagnostic subdivision and classification of the patients who have met the inclusion criteria for schizophrenia or a related disorder. If schizophrenia is, genetically and aetiologically, a heterogeneous group of disorders – an idea which goes back to Bleuler (1911) and Kraepelin (1920) and has been resuscitated by modern biological research (McGuffin, 1988) – it is important to know if any particular diagnostic subdivision of the sample would provide 'points of rarity' (Kendell & Brockington, 1980) that may help to identify real discontinuities or well defined syndromes.

Subdivision by CATEGO class S+ (first-rank symptoms)

In the exploratory analyses, carried out in the context of the present study, a special attempt was made to establish how different patients assigned to CATEGO class S+, which by definition identifies patients with highly characteristic symptoms of schizophrenia (Schneider, 1959) were from patients assigned to CATEGO classes S?, P, and O. The results reported in the preceding chapters show clearly that CATEGO S+ patients constituted either the majority, or a substantial minority, of the patients meeting the inclusion criteria in all the centres. The comparisons between S+ and non-S+ cases in the total study population can be summarized as follows.

Variables on which S+ and non-S+ cases differ

(i) Percentage of cases with clinical diagnosis of schizophrenia (87% of S+ and 81% of non-S+).
(ii) Percentage of cases with any one of the clinical diagnoses required for inclusion (95% of S+ and 89% of non-S+).
(iii) Percentage scores on all PSE psychotic symptoms (uniformly higher in S+ than in non-S+).
(iv) History of convulsions (2–3 times more likely in S+ than in non-S+).
(v) History of emotional or conduct problems in childhood (19% of S+ and 14% of non-S+).
(vi) History of emotional or conduct problems in adolescence (27% of S+ and 20% of non-S+).
(vii) History of psychotic illness in the mother (in 50 out of the 108 S+ patients with at least one parent mentally ill, compared to 24 out of 67 non-S+ patients).

Variables on which S+ and non-S+ do not differ

(i) Percentage scores on PSE affective symptoms.
(ii) Mode of onset.
(iii) Pattern of course.

The evidence summarized above does not lend sufficient support to a notion of a discrete entity of 'nuclear' schizophrenia, qualitatively different from the other syndromes exhibited by the patients in this study. As previously shown (p. 37) the S+ patients have more florid 'positive' psychotic symptoms. Such patients may represent one extreme of a continuum of psychopathology spanning all the distance between oligosymptomatic cases, manifesting predominantly deficits and 'negative' symptoms, and cases with the full-blown picture of schizophrenic psychosis. In this sense, the presence of

Schneider's first-rank symptoms can be regarded as an index of severity of 'positive' psychotic disturbances in schizophrenic patients. The uniform occurrence of such symptoms in patients belonging to different cultural environments provides a justification for their use as epidemiological tools.

Subdivision by acute/non-acute clinical subtype

Mode of onset, i.e. the time elapsed since the first appearance of an unequivocally psychotic manifestation and the point at which a recognizable clinical syndrome or symptom complex is present, emerged as an important variable in a number of the analyses described in previous chapters. This raises the question of a possible existence in the study population of a subgroup of cases which is not merely a variant of the manifestation of the same basic disorder, i.e. schizophrenia but a psychotic condition *sui generis* which may be distinct from schizophrenia in several aspects. If this were the case, this group of acute illnesses should be classified separately from 'mainstream' schizophrenia.

In order to test this proposition, the age and sex distribution of the disorders diagnosed in the centres as acute schizophrenic episodes was examined in the developing and the developed countries, and was compared with the distribution for patients with all other schizophrenic diagnoses. The results (Tables 5.3 and 5.4) indicate that: (i) in both developed and developing countries the male/female ratio in the group of patients with acute schizophrenic episodes is lower than in the group of patients with other schizophrenic diagnoses (0·9 and 1·2 respectively for acute, 1·2 and 2·0 respectively for all other schizophrenia), i.e. the proportion of women is higher in the acute group; (ii) there is a relative excess of patients in younger age groups (15–24) among the cases diagnosed as acute schizophrenic episodes in both developing and developed countries.

Table 5.3. *Sex ratio in (a) schizophrenic psychoses (excluding acute) and (b) acute schizophrenic episode, by developed countries and developing countries*

	Schizophrenic psychosis (excluding acute)		Acute schizophrenic episode	
Setting	M	F	M	F
Developed countries	54·4 (245)	45·6 (205)	48·6 (34)	51·4 (36)
M:F	1·2		0·9	
Developing countries	66·2 (200)	33·8 (102)	53·9 (110)	46·1 (94)
M:F	2·0		1·2	

Table 5.4. *Age group distribution of (a) schizophrenic psychoses (excluding acute) and (b) acute schizophrenic episode, by developed countries and developing countries*

	Schizophrenic psychoses (excluding acute)		Acute schizophrenic episode	
Age group	Developed	Developing	Developed	Developing
15–24	44·2	50·0	60·0	72·6
25–34	33·1	34·8	21·4	23·5
35–44	15·1	12·9	11·4	3·4
45–54	7·6	2·3	7·1	0·5

Table 5.5. *Most common symptoms at initial examination in patients with centre diagnosis of acute schizophrenic episode, by developed countries and developing countries*

Most common symptoms (occurring in ⩾ 30% of patients)			
Developed countries	%	Developing countries	%
1 Systematization of delusions	62·9	1 *Voice speaking to subject*	51·5
2 *Depressed mood*	55·7	2 Systematization of delusions	47·5
3 Delusions of reference	51·4	3 Acting out delusions	47·1
4 Acting out delusions	51·4	4 Delusions of reference	43·1
5 *Delusional misinterpretation and misidentification*	44·3	5 Delusions of persecution	42·6
4 Delusions of persecution	44·3	6 *Visual hallucinations*	35·8
7 *Evasiveness*	44·3		
8 *Preoccupation with delusions and hallucinations*	38·6		
9 *Delusional mood*	35·7		
10 *Morning depression*	32·9		

Further, the most common symptoms (those occurring in 30% or more of the patients) were tabulated for acute schizophrenic episodes in the developed and the developing countries (Table 5.5). The symptoms which appear among the most common ones in one type of setting but not in the other are in italics. Out of 10 symptoms which appear in over 30% of the patients in the developed countries, 4 occur with the same frequency in the developing countries; and out of the 6 common symptoms in the patients in developing countries, 4 are also common in patients in the developed countries. Thus, considerable symptomatological similarity exists between the disorders diagnosed as acute schizophrenic episodes in the two types of setting.

Next, the most common symptoms (occurring in 30% or more of the patients) were tabulated for acute schizophrenic episodes and for all other schizophrenia subtypes, for all patients regardless of setting. Seven out of the 8 common symptoms in the acute group were identical with the most common symptoms (their total number also was 7) in the group of other schizophrenia subtypes (Table 5.6). The results of this analysis, therefore, do not support the proposition that the acute schizophrenic episodes included in the present study represent a type of disorder that is nosologically different from schizophrenia.

Table 5.6. *Most common symptoms at initial examination in patients with centre diagnosis of schizophrenic psychosis (excluding acute) and acute schizophrenic episode (all centres)*

Most common symptoms (occurring in ⩾ 30% of patients)			
Schizophrenic psychoses (excluding acute)	%	Acute schizophrenic episode	%
1 Systematization of delusions	53·7	1 Systematization of delusions	51·5
2 Acting out delusions	50·0	2 Acting out delusions	48·2
3 Delusions of reference	49·1	3 Voice speaking to subject	45·6
4 Delusions of persecution	44·1	4 Delusions of reference	45·3
5 Depressed mood	33·9	5 Delusions of persecution	43·1
6 Voice speaking to subject	32·7	6 *Visual hallucinations*	38·1
7 *Delusional misinterpretation and misidentification*	32·6	7 Depressed mood	30·3
8 Evasiveness	32·6	8 Evasiveness	30·3

HAS NEW KNOWLEDGE BEEN ADDED TO THE UNDERSTANDING OF THE COURSE AND OUTCOME OF SCHIZOPHRENIA?

Being separated by nearly a decade from the follow-up data collection phase of the IPSS, the Outcome study has provided data which, on the one hand, confirm and refine some of the important conclusions reached in that previous study and, on the other hand, contribute new knowledge about certain aspects of the prognosis of schizophrenia.

Diversity of patterns of course

First, it has again been clearly demonstrated that the course of conditions meeting clinical criteria for schizophrenia is far from being uniform and does not conform to a single pattern. In a substantial proportion (over 50%) of the cases the psychotic disturbance is limited to a single episode of a varying duration (several weeks to several months) which may be followed either by a complete remission in which the patient is practically symptom-free, or by a symptomatic but non-psychotic state characterized by affective and neurotic disturbances or by mild aberrations or changes of personality and behaviour. Undoubtedly, the relatively high frequency of the complete recovery after a psychotic episode qualifying for a diagnosis of schizophrenia (approximately every fourth patient in the developing countries, and every seventh in the developed countries) is one of the most important findings of this study. Although this pattern of course occurs more frequently in the developing countries, it is not uncommon in the developed countries.

In a proportion of the cases (about 31%) the pattern of course is episodic, with two or more psychotic attacks, each followed by a remission which may be complete or incomplete, in the sense referred to above. This pattern of course in schizophrenia bears a similarity to what is commonly accepted to be the characteristic course of the affective disorders but the symptomatology of these cases is not necessarily of the schizoaffective type.

In yet another percentage of the patients (about 15%) the course of the psychotic disorder is continuous and unremitting, leading to severe impairment. These cases are more frequent in the developed countries than in the developing countries, but it is more important to recognize that they occur in both types of setting and that their clinical characteristics are very similar. Thus, the Outcome study did not identify any particular pattern of the course and outcome of schizophrenic illnesses which could be regarded as specific to a given area or culture. The descriptive categories used to classify the di-

versity manifest in the evolution of schizophrenic disorders were equally applicable to the patient series in the developing and in the developed countries.

Higher frequency of good outcome in the developing countries

The Outcome study replicated in a clear and, possibly, conclusive way the major finding of the IPSS, that of the existence of consistent and marked differences in the prognosis of schizophrenia between the centres in developed countries and the centres in developing countries. On five out of six of the measures and dimensions of two-year course and outcome which have been used in the analyses reported here (pattern of course, proportion of the follow-up period in complete remission, proportion of the time during which the patient was on anti-psychotic medication, proportion of the follow-up period spent in psychiatric hospital, and proportion of the follow-up during which the social functioning of the patient was unimpaired), patients in the developing countries show a more favourable evolution than their counterparts in the developed countries (the only dimension showing no difference was the percentage of the follow-up period spent in psychotic episodes). As demonstrated by the multivariate statistical analysis, these differences between patients in the two types of setting cannot be explained by other variables and remain highly significant when such possible influences are controlled for. It can now be said with a fair amount of confidence that they are not the result of differing sample composition in the two groups of centres, in the sense of a selection bias in favour of more pre-inclusion chronicity in the developed countries and more recent onsets in the developing countries. In this study, the average length of the illness prior to inclusion into the study did not differ significantly between the developing and the developed countries.

A more complex issue is the possibility that the clinical conditions meeting the inclusion criteria of the study in the two types of setting may be heterogeneous and include varying proportions of aetiologically and genetically different disorders which may be distinguishable from one another at the level of the phenotype, i.e. the symptoms and syndromes. This possibility exists but it cannot be properly examined or tested at the present time, in the absence of established genetic markers, indicators of aetiology or other underlying mechanisms of disease. It is, however, possible to reject another hypothesis which can be formulated in clinical and descriptive, rather than biological terms. This is the conjecture that the patient sample in the developing countries might contain an excessive number of cases of so-called acute transient psychoses, for which some evidence exists now that they are both clinically and aetiologically distinct from schizophrenia. The evidence reviewed in a preceding section of this chapter is sufficient to reject the hypothesis that an inclusion of atypical transient psychotic illnesses among the schizophrenic cases in the developing countries could explain the better course and outcome in these areas. Moreover, it can be shown that the difference in the course and outcome of schizophrenia between the two groups of centres clearly persists if the comparison is limited only to cases of schizophrenia with a gradual or insidious onset. Table 5.7 shows that while less than 30% of the gradual onset cases in developed countries had 'mild' patterns of course, this figure was over 40% for patients with the same type of onset in the developing countries. On the other hand, 53% of the gradual onset patients in developed countries, compared with 43% in developing countries, had a 'severe' pattern of course.

Table 5.7. *Pattern of course (2 year-follow-up) by type of onset and setting (percentages)*

Setting	Type of onset	Pattern of course: Mild	Intermediate	Severe
Developed countries	Acute	52·1	25·1	22·6
$\chi^2 = 40{\cdot}3$	Subacute	41·3	23·9	34·7
$P < 0{\cdot}001$	Gradual	29·8	17·5	52·6
	All types	38·9	21·1	39·8
Developing countries*	Acute	62·0	21·0	16·9
$\chi^2 = 26{\cdot}4$	Subacute	58·7	23·8	17·4
$P < 0{\cdot}001$	Gradual	40·2	16·3	43·4
	All types	55·7	20·2	24·0

* Ibadan excluded.

Having excluded, for lack of support by the data described in this report, the explanation of the observed difference between the prognosis of schizophrenia in developing and in developed countries as an artefact, a strong case can be made for a real pervasive influence of a powerful factor which can be referred to as 'culture'. Unfortunately, neither the IPSS nor the Outcome study could penetrate in sufficient depth below the surface on which the impact of this unknown factor was established – tentatively in the IPSS and definitively in the present study. Although other components of the Outcome study (e.g. the investigation on the 'expressed emotion' in families of schizophrenic patients in Aarhus and Chandigarh, Wig *et al.* 1987; Leff *et al.* 1990) demonstrated important differences at the level of day-to-day social interaction of patients and key figures in their environment in the two types of setting, it is unlikely that the variation in course and outcome between developing countries and developed countries could be reduced to a single variable. The contribution of the present study, therefore, is not in providing the answer but in clearly demonstrating the existence of the question.

Predictors of course and outcome

By using a log-linear model in the analysis of the relationship between a number of variables which had been assessed on initial examination and variables characterizing the two-year course of the disorder, it has been possible in the Outcome study to refine the data on the prediction of course and outcome. Overall, there is good agreement between the conclusions concerning predictors which were reached in the IPSS and the conclusions about prognostic indicators in the present study. Although the instruments for collection of previous psychiatric and social history data were different in the two studies, some of the potentially predictive variables, such as type of onset, marital status, or length of previous illness were assessed in a similar manner (but more systematically and in greater detail in the Outcome study). There is further a high level of comparability for the dependent variables in the analysis of predictors in the two studies, as pattern of course and percentage of the follow-up in psychotic episodes were defined and assessed in a similar way. However, while stepwise multiple regression was the main tool of predictor data analysis in the IPSS, a log-odds (log-linear) model was selected for the Outcome study. The latter is better suited to the handling of psychiatric and social data (which are often of a categorial nature) because it makes no distributional assumptions. Besides, upon examining the estimated partial derivatives in the log-linear model, the contribution of individual predictors to the course and outcome variables can be understood in terms of percentage point differences, which is a simpler and perhaps clearer 'mental representation' of the mathematical function.

The results of the log-linear analysis highlight the key significance of two predictor variables: the type of onset of the disorder and the type of setting (developed or developing country). Because of the strong association of these two predictors with the pattern of course, their effects had to be controlled for in the estimation of the contribution of each one among the remaining explanatory variables. While it is true that both the type of onset and the developing/developed country dichotomy had already been shown to be predictors of course and outcome in the IPSS, their overriding importance has been put into a much sharper focus by the analysis reported in chapter 4 of this report. It should be emphasized again that their contribution to the prediction of course and outcome is independent; i.e. the better prognosis of schizophrenic disorders in the developing countries is not reducible to the relative excess of acute onsets in such settings, nor to any other of the predictor variables tested in the model. Type of onset, therefore, appears in the light of the findings of the present study, as one of the critical variables in schizophrenia research.

The Outcome study findings confirm the relatively modest but still quite definite prognostic significance of the diagnostic classification of schizophrenic disorders according to ICD-9 subtypes. The direction in which the individual subtypes predict the pattern of course is consistent with previous knowledge and data. While the hebephrenic subtype is associated with the worst prognosis, the subtypes characterized by acuteness of onset, presence of affective symptoms, and catatonic disturbances (i.e. 295.4, 295.7 and 295.2) are linked with the best chances of recovery.

Of the remaining predictors, variables such as sex, marital status, and persistent adjustment problems in adolescence also seem to confirm previous knowledge. What is new is the finding that frequency of contacts outside the family (close and casual friends) is just as useful a

predictor as the frequency of contacts with family members, while avoidance of the patient by others is not (the avoidance of the patient by family members on the other hand is a useful predictor). Being based on a large patient series in different cultures, this finding may be of considerable potential interest for the understanding of the nature and effects of social support networks in schizophrenia. It certainly raises the important question about the interpretation of other research evidence, collected in the present study, on the role of 'expressed emotion' in the family in the determination of the pattern of course.

The predictor analysis demonstrated further that the proportion of the follow-up period during which patients are in incomplete remissions is that aspect of the course of schizophrenia which is most clearly associated with the difference between the settings (developing *versus* developed countries). Being in a developed country was a strong predictor of not attaining a complete remission. It seems, therefore, that a major part of the difference in the prognosis of schizophrenia in the two kinds of setting may be reduced to the failure of many patients in the developed countries to attain or maintain a complete remission of symptoms.

An unexpected finding which calls for further exploration is the prediction of poor course and outcome by a history of 'street' drug use (the initial expectation was that drug use may be a triggering factor in the precipitation of relatively benign schizophreniform illnesses). The high incidence of reported drug abuse among study patients in three of the centres of the study (Honolulu, Rochester, and Aarhus), may be an indication of an increase in the frequency of the combined occurrence of psychotic illness and drug use. While there is no reason to regard these cases in the Outcome study as drug-induced psychoses, the phenomenon merits careful investigation.

IMPLICATIONS OF THE FINDING OF SIMILAR INCIDENCE RATES OF SCHIZOPHRENIA IN DIFFERENT GEOGRAPHICAL AREAS

A major new finding of the study is that incidence rates for various levels of definition of schizophrenic disorders are surprisingly similar, especially for the most restricted definition by CATEGO S+ class.

Apart from two centres with differing patterns of age- and sex-specific rates, the rates even for the broadest defined level varied among the six other centres at most by a factor of 2–2·5. By inclusion of schizophrenia related disorders by clinical diagnosis or by CATEGO class O? considerable variations among centres would be expected because of varying incidence of acute or reactive disorders or drug induced disorders. Whether the actual variation particularly in the Chandigarh and Moscow centres is explained by the inclusion of such cases is difficult to determine. For the Moscow centre the variation is mainly caused by high female rates in higher age groups which hardly would be caused by reactive or drug induced cases, and the possible role of a different nosology of schizophrenia in this centre does not appear to offer an explanation either because the variation appears also at the SPO+ level. For the Chandigarh centre the rural sample shows the highest rates causing the great differences in the variation which may have a number of possible explanations, such as inclusion of acute or reactive or organic cases with SPO+ level symptoms. The Chandigarh urban sample however showed lower rates and the pattern of age and sex specific rates shows more resemblance to patterns in most of the other centres.

At the restricted S+ diagnostic level the differences diminish and the variation is not greater than may be explained by chance variation. The lower number of patients by the more restrictive level does not explain the lower variation which rather would be expected to increase by chance fluctuations. Extending the case finding periods or doubling up the numbers with unchanged rates would of course increase the power of the statistical evaluation and might have been able to detect significant differences also at the restricted diagnostic level. However, the actually observed rates at the various diagnostic levels appear to differ among the centres within a modest range pointing more to similarity than variability of the incidence of schizophrenia and schizophrenia-like disorders.

The importance of the differences depend on the point of view. For health administrations the differences of the broadly defined diagnostic level is important for the delivery of health care

to a number of patients which may vary with the factor of two or three among centres. For aetiological studies exploring the cause of schizophrenic disorders, the similarity of incidence rates at the S+ CATEGO class levels is an important finding.

The absence of marked variation in the incidence of schizophrenia will not easily lend itself to an interpretation, unless the nature of the relationship of the schizophrenic phenotype to the underlying causes and pathophysiology of the disorder is clarified. Linked to this is the question whether schizophrenia is a single disease entity or a heterogeneous group of conditions which exhibit a 'common final pathway'.

In a lucid overview of the state of knowledge in this respect, Bleuler (1981) classified the different views on the subject into three 'schools'. The first, which he termed 'elementary' school, adheres to the formula 'one disease – one cause'. The second, or 'middle' school regards schizophrenia as 'many diseases, each with its own causes'. The third, or 'high' school, would see in schizophrenia neither a single disease, nor a collection of single diseases, but rather a manifestation of a developmental disorder in which 'multiple influences shape symptomatology and course'. This position goes full circle back to the views of Kraepelin (1920) who, at the end of his career, came to regard schizophrenia as 'a common reaction of mankind to the most varied forms of noxious events'. According to Kraepelin, '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 hereditary factors make certain areas more susceptible and accessible to pathological stimuli'.

Current hypotheses about schizophrenia as a neurodevelopmental disorder, which build on recent advances of cerebral morphology, genetics and pathophysiology (e.g. Murray & Lewis, 1988) in fact echo the conjectures referred to above. Such a model would be in agreement with the epidemiological data. If schizophrenia is conceptualized not as a single disease but as a 'common final pathway' for a variety of cerebral disorders and neurodevelopmental lesions, similar rates of its incidence in different populations could be seen as the expression of a more or less uniformly distributed liability for a schizophrenic type of reaction to different causes. This liability must have a genetic basis which may be more complex than currently assumed. A 'nuclear' schizophrenic syndrome (identified by CATEGO S+ in the present study) – with its clinical consistency and uniform occurrence – in different cultures, may be the manifestation of a specific segment of a complex genotype with a much wider range of phenotypical expression.

However, the question whether the apparently similar rates of manifestation of schizophrenic syndromes in different populations are primarily due to a uniformly distributed genetic liability, or to some ubiquitous constellation of environmental factors interacting with it, or to a similarity in expression of genetically different disorders, should be addressed in future research. The present study has developed an extensive database which fills a number of important gaps in the descriptive phenomenology and epidemiology of schizophrenia worldwide. As linkage studies and genome mapping techniques are now preparing the ground for a 'molecular' epidemiology of schizophrenia, a new role may be emerging for comparative epidemiological research across different populations and geographical areas: that of guiding neurobiology to more clearly defined targets, taking into account the ultimate role of culture as the context in which gene-environment interactions shape the clinical picture of human disease.

Conclusion: A synopsis of the main findings

1 The study on Determinants of Outcome of Severe Mental Disorder (Outcome study) is a cross-cultural investigation, coordinated by WHO, of schizophrenic and related disorders in 13 geographical areas in 10 countries (Colombia, Czechoslovakia, Denmark, India, Ireland, Japan, Nigeria, the Union of Soviet Socialist Republics, the United Kingdom, and the United States of America).

2 The study is based on an initial examination and two follow-up examinations, at annual intervals, of 1379 patients. Of the total number, 78·2% completed the follow-up and were re-assessed two years after the initial examination.

3 The patients included in this study were new cases, in the sense that they had contacted a 'helping agency' for their mental health problem for the first time in their lives during the three months preceding the initial examination, and had practically no previous exposure to psychiatric treatment or care. The reasons for making a first contact with a 'helping agency' were similar in the developing and the developed countries (behaviour perceived as 'odd' and feared violent behaviour towards self or others being cited in about 90% of the cases). The mean length of previous illness (i.e. prior to inclusion into the study) was practically the same for patients in developing countries and patients in developed countries. The majority (86%) of the patients were recruited for the study within less than a year of the first appearance of symptoms.

4 In 39% of the cases the first help-seeking contact was made with a psychiatrist; however, especially in the developing countries, traditional medicine is a frequent resource in the event of mental disorder and is often utilized simultaneously with the services of 'Western' mental health care. It has been estimated that about 200 cases eligible for this study would have been missed if traditional practitioners had not cooperated in case-finding.

5 There was a considerable amount of similarity in the early behavioural manifestations of psychotic illnesses across the centres. In both developing and developed countries 'negative' behavioural disturbances (neglect of usual activities, social withdrawal) were described more often as the earliest perceived signs of illness than frank psychotic manifestations such as talk of persecution, harm or bewitchment, or behaving as if hearing voices. Family members and key informants in the community appeared to be sensitive observers and served well as a case-finding resource in the majority of the centres.

6 Of all included cases, 82% were assigned to CATEGO classes S, P, or O which, together with a clinical ICD diagnosis of schizophrenia and schizophrenia-related disorders (paranoid psychoses, reactive paranoid and schizophreniform psychoses, unspecified psychoses, alcohol and drug induced psychoses with hallucinatory or paranoid symptoms, schizoid and paranoid personality disorders) were considered to constitute a broad group of schizophrenia and related disorders in this study. The classification of a patient into the broad group of schizophrenic disorders required either one of the ICD diagnoses listed above or a CATEGO class S, P, or O. Between 60% and 95% of the patients in the different centres met both criteria. It should, however, be emphasized that the inclusion of cases into the study through a screening process was based on specified symptoms and behaviours, and not on diagnosis.

7 More than one half (56%) of the study population had CATEGO class S+ ('nuclear' schizophrenia), defined by the presence of one or more of Schneider's first-rank symptoms (Schneider, 1959). These patients were found to have high scores on all types 'positive' psychotic symptoms, and could be considered to be a more severely disturbed subgroup than the rest of the patients.

8 The PSE profiles of the patients meeting the 'broad' inclusion criteria of this study were similar in the developed and the developing countries. In the latter, visual hallucinations tended to occur more often, and in the former, affective symptoms, especially depression, were more common. However, these differences could be regarded as relatively insignificant, considering the great similarity in the scores of the remaining symptoms.

9 Schizoid traits: sensitivity, suspiciousness and reserve, were described as manifest during adolescence in a high proportion of the patients. However, contrary to expectations, presence of 'positive' pre-morbid personality traits was more frequent in patients who were classified as CATEGO S+.

10 The annual incidence of new cases of 'broadly' defined schizophrenia was in the range between 1·5 and 4·2 (both sexes) per 100000 population at risk (age 15–54). The incidence of schizophrenia defined by CATEGO class S+ was in the range between 0·7 and 1·4 per 100000. The morbid risk (expectancy) for schizophrenia, determined on the basis of the incidence data, is between 0·5 and 1·72% for the 'broad' diagnostic category, and between 0·26 and 0·54 for CATEGO S+. The incidence of 'broadly' defined schizophrenia was highest in India (both the rural and the urban area of Chandigarh). The differences between the incidence rates for the 'broad' diagnostic category of schizophrenia in the different centres were significant and indicate the necessity of future studies in some of the centres, particularly the Chandigarh areas, to further explore the nature of their high incidence rates. In every centre, the incidence rates tended to decrease as more specific definitions of 'caseness' for schizophrenia were applied. At the level of CATEGO S+, there were no significant differences across the study areas.

11 In all the study areas, the age- and sex-specific curves of the incidence of schizophrenia followed a similar pattern. It was demonstrated that in developed and in developing countries alike, the onset of schizophrenia tended to occur at a later age in females as compared to males. The similarity of age- and sex-related patterns of onset of schizophrenia across the study areas is a strong evidence that the same basic type of disorder has been identified and investigated in the different cultural settings of the study.

12 The majority of the patients in the study had a remitting pattern of course over the two years of follow-up: 50·3% had a single psychotic episode and a further 31·1% had two or more psychotic episodes followed by remissions. Only 15·7% of the patients had an unremitting, continuous psychotic illness. The remitting patterns were more common among patient populations in the developing countries.

13 On five out of six course and outcome dimensions patients in the developing countries had a markedly better prognosis than patients in the developed countries. The tendency for a more favourable course and outcome was not limited to acute schizophrenic episodes; it was also clearly present in the subset of cases which had a gradual or insidious onset of schizophrenia. The only variable which did not distinguish clearly between patients in developing countries and patients in developed countries was the proportion of the follow-up period during which patients were in psychotic episodes. On the other hand, the variable on which patients in the two kinds of setting differed most was the proportion of the follow-up period during which patients were in incomplete remissions: the mean percentage of time in such state was considerably higher for patients in the developed countries.

14 About one third of all the patients in the study were never admitted to a psychiatric hospital; of those admitted, the majority spent only brief periods in hospital treatment. On the other hand, 95% of the total study sample were prescribed neuroleptic medication for varying lengths of time in the course of the study; patients in the developed countries were prescribed anti-psychotic drugs over longer periods of time than patients in the developing countries.

15 The different sets of inclusion criteria ('broad' *versus* 'restrictive') did not result in the selection of patients differing according to their prognosis. The CATEGO class assigned on initial examination had no prognostic significance; however, the clinical subtyping of schizophrenic disorders according to ICD-9 criteria was associated with some significant differences in course and outcome. The hebephrenic and paranoid subtypes tended to have the worst course and outcome, while the acute schizophrenic episodes had the best course and outcome.

16 Type of onset (i.e. acute, subacute, and gradual) and setting (developing country or

developed country) were the most important predictors of several dimensions of the two-year course and outcome. Other significant predictors were: clinical diagnosis on initial examination, marital status, sex, adjustment in adolescence, frequency of contact with friends, and history of use of 'street' drugs. The use of a log-linear model for the identification and assessment of predictors has resulted in prognostic tables which may be further tested in clinical trials.

17 The study described in this report will raise a number of new research questions. Schizophrenia remains an entity defined almost exclusively by its clinical symptoms and their characteristic evolution over time. No external validating criteria for the diagnosis have yet been established, in spite of a number of suggestive biological findings, among which genetic data appear to be the most consistent. The study of the epidemiology of a disorder can provide critical leads to the understanding of causes and risk factors. In the instance of schizophrenia, this has not occurred because of continuing uncertainties due to the absence of reliable diagnostic indicators and markers, and of a sharp demarcation between its symptoms and the symptoms of other psychiatric conditions. This hampers the application of multidisciplinary approaches. The collaborative studies coordinated by WHO are contributing to the resolution of such difficulties by creating an international, cumulative clinical and epidemiological database on schizophrenia and related disorders worldwide.

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