Psychological

MONOGRAPH SUPPLEMENT 20

Schizophrenia: manifestations, incidence and course in different cultures
A World Health Organization Ten-Country Study

by A. Jablensky, N. Sartorius, G. Ernberg, M. Anker, A. Korten, J. E. Cooper, R. Day and A. Bertelsen

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This monograph presents the findings of a WHO Collaborative Study on the Determinants of Outcome of Severe Mental Disorders (DOS). The study was designed to investigate further some of the findings of the WHO International Pilot Study of Schizophrenia (IPSS) which produced the unexpected finding that patients suffering from schizophrenia in the centres in developing countries appear to have a more favourable outcome at both two and five years follow-up than initially similar patients in centres in developed countries. The DOS was carried out in field centres in Aarhus (Denmark), Agra and Chandigarh (India), Cali (Columbia), Dublin (Ireland), Honolulu and Rochester (United States of America), Ibadan (Nigeria), Moscow (USSR), Nagasaki (Japan), Nottingham (United Kingdom), and Prague (Czechoslovakia). Six of these centres had also taken part in the IPSS.

One of the major achievements of the IPSS had been the demonstration that large-scale cross-cultural studies using standardized methods of interviewing, symptom rating and diagnosis are possible. The study reported here rested upon the same methodological foundations but used an epidemiological approach. In each of the twelve centres of the DOS, all individuals from a defined catchment area making a lifetime first contact with specified psychiatric, medical or other agencies because of symptoms of a possibly schizophrenic illness were identified, assessed, and followed up for two years.

The finding of a better outcome of patients in developing countries was confirmed, as was the existence of a substantial proportion of patients (often more than half) with undoubted initial schizophrenic symptoms but a good outcome at two years. About one-third of all patients in the study were never admitted to a psychiatric hospital, and of those that were admitted the majority were in hospital for only short periods.

The Study also produced evidence about the incidence rates of schizophrenia. Significant differences were found between centres in the incidence of schizophrenia using a broad definition, although the rates ranged only from 1·5 to 4·2 per 100000 population aged 15–54. In contrast, the incidence of schizophrenia using a narrow definition based on the presence of a limited number of 'classical' symptoms in the present mental state (category S+ of the CATEGO program derived from the PSE-9 interview) was not significantly different between centres.

This study confirms that schizophrenic illnesses are ubiquitous, appear with similar incidence in different cultures and have clinical features that are more remarkable by their similarity across cultures than by their difference. They are illnesses with variable outcomes which are more favourable in the developing countries and depend on genetic, developmental and environmental influences whose exact nature, interaction and relative importance have yet to be identified.

Psychological Medicine

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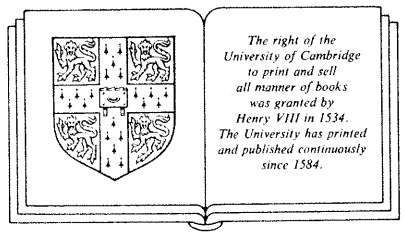

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At WHO Headquarters, Geneva, the study was coordinated by N. Sartorius (principal investigator) and A. Jablensky (co-principal investigator).

A list of other staff who participated in the project is given on page v.

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SYNOPSIS In the 1960s the World Health Organization (WHO) carried out an Internationa Study of Schizophrenia (IPSS), a transcultural investigation of more than 1200 patients i countries: China, Colombia, Czechoslovakia, Denmark, India, Nigeria, United Kingdom, and USSR. The study established that large-scale international psychiatric studies are feasi produced standardized instruments allowing reliable assessment of people suffering from s disorders in different cultures and created a network of centres able and willing to work to in psychiatric research.

The study established that schizophrenic disorders exist in different parts of the world an the features of their clinical conditions were marked by their similarity rather than differenc follow-up of the patients over a period of five years demonstrated that a significant proport people in whom a schizophrenic syndrome had been diagnosed recovered well and th percentage of patients with a good outcome was higher in developing than in developed cou This finding needed confirmation because of its potential significance for public health.

A few years later WHO therefore launched a second study – this time aiming to produce est of incidence of schizophrenia in different cultures and definitive evidence about the cours outcome of schizophrenia in different parts of the world. Twelve centres in ten co participated in this work (Aarhus (Denmark), Agra and Chandigarh (India), Cali (Colo Dublin (Ireland), Honolulu and Rochester (United States of America), Ibadan (Nigeria), M (USSR), Nagasaki (Japan), Nottingham (United Kingdom), and Prague (Czechoslovakia)). them (Aarhus, Agra, Cali, Ibadan, Moscow and Prague) had also taken part in the IPSS. The was supported – as was the case with IPSS – by WHO, the United States National Instit Mental Health and the research centres.

In each of the centres arrangements were made to identify and assess over a period of two all individuals who met four inclusion criteria: i.e. (i) were aged between 15 and 54 years; (resided for at least six months in the area; (iii) had shown at least one overt syn (hallucinations, delusions, qualitative thought or speech disorders or gross behaviour normalities) or at least two abnormalities suggestive of psychotic disorder (e.g. episodic excitement, significant social withdrawal, overwhelming fear); and (iv) had recently made a f lifetime contact with a helping agency. Clinical evidence of gross organic cerebral disor previous contacts with psychiatric or other agencies because of mental disorders similar current one excluded the patient from the study. Over a period of two years the centres a standardized screening and assessment procedures according to a commonly accepted proto seven centres it was possible to follow the protocol to the letter: Aarhus, Chandigarh, D Honolulu, Moscow, Nagasaki and Nottingham. In the five other centres certain modificatio to be introduced. This made it possible to obtain incidence figures in 7 of the sites and co information about clinical characteristics of people suffering from schizophrenic syndromes fr the 12 sites.

Patients were examined using a set of standardized instruments selected among the av research tools or developed especially for this study. The reliability of psychiatric assessme tested and maintained by conducting joint interviews and by rating taped interviews. Equ language versions of the instruments were produced for each of the centres. They dealt w mental state, psychiatric history, social characteristics and other variables relevant for t description of the patients.

In all, 1535 patients passed the initial screening. From that group some patients had excluded either because they had had previous contacts with psychiatric services or for dia reasons. This resulted in a cohort of 1379 patients who were examined in detail and followed u a period of two years.

The main findings of this study can be summarized as follows.

1. The study demonstrated that follow-up examinations and comparative longitudinal re in general are feasible in different types of countries. Nearly 80% of all patients could be fo up and assessed two years after the initial examination. The study confirmed that larg international collaborative studies of psychiatric disorders are feasible and that psych

belonging to different cultural backgrounds can be trained to use standardized research instruments in a reliable way.

2. The reasons for patients making these lifetime first contacts were similar in developed and developing countries. Of all included cases, nearly 80% were considered to constitute a broad group of schizophrenic and related disorders. More than half of the study population showed a syndrome of nuclear schizophrenia defined by the presence of specific symptoms (Category S+ of the CATEGO program derived from the PSE-9 mental state examination).

3. 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 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. However, in every centre, the incidence rates tended to decrease as more specific definitions of 'caseness' for schizophrenia were applied and at the level of CATEGO S+, there were no significant differences between the study areas.

4. 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 supports the notion that under the diagnostic category of schizophrenia the same disorder has been identified and investigated in the different cultural settings of the study.

5. 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 more favourable outcome and remitting patterns were significantly more common amongst the patients in the developing countries.

6. 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. The difference in outcome between developing and developed countries remained significant when patients with acute onset of disease and those with insidious onset were studied separately. Other significant predictors were: clinical diagnosis on initial examination, marital status, sex, adjustment in adolescence, frequency of contact with friends and history of the use of 'street' drugs.

7. Interpretation of the findings of this study are restricted by the comparatively small proportion of the variation in both incidence rates and measures of outcome that can be explained by the descriptive clinical differences among the patients. Much more social and family information was collected than in the IPSS, but even so, no fundamentally different findings emerged. It is clear that 'culture' is confirmed as an important determinant of outcome, but exactly how the influences implied by this general concept impinge upon the behaviour and experiences of individuals and families requires further study. In the absence of reliable biological markers, schizophrenia can only be described by clinical characteristics; this means that further epidemiological and cross-cultural investigations, using an interdisciplinary approach to the study of smaller sub-groups and specific clinical issues, are still likely to form a large part of the most productive strategy for research in the near future.

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Introduction

In the late 1960s the World Health Organization initiated the International Pilot Study of Schizophrenia (IPSS), a transcultural psychiatric investigation of 1202 patients in nine countries – China, Colombia, Czechoslovakia, Denmark, India, Nigeria, USSR, United Kingdom and USA. The study was coordinated by WHO and funded jointly by WHO, the National Institute of Mental Health (NIMH) of the United States, and the field research centres. It was designed to lay scientific groundwork for future epidemiological studies of schizophrenia and other psychiatric disorders. Some of the aims of the IPSS were concerned with methodology: to establish the feasibility of large-scale international psychiatric studies, to develop standardized instruments for reliable assessment of patients in different cultures, and to train investigators in developing and developed countries to use such techniques to make comparable observations. Other aims of the project were related to substantive issues about schizophrenia: to explore whether schizophrenic disorders exist in different parts of the world, to identify similarities and dissimilarities between patients diagnosed as schizophrenics in the different centres, and to investigate whether the course and outcome of schizophrenic disorders differ from country to country. The 1202 patients, in the age range 15 to 44, were selected in accordance with screening criteria which excluded cases of gross organic cerebral pathology, chronic conditions of long duration, sensory defects and mental retardation. Each patient was given a detailed clinical and social evaluation at the point of intake, and the full assessment was repeated two years, five years and in some centres 10 years after inclusion in the study.

The results of the IPSS have been described in a series of publications (WHO, 1973, 1979; Sartorius *et al.* 1977, 1987; Jablensky, 1987; Leff *et al.* in press). In addition to advancing the methodology of comparative research in the major psychiatric disorders, the project produced evidence that similar syndromes of schizophrenia and other functional psychotic illnesses occur in the different cultures represented in the study. A striking finding which emerged from the follow-up stage of the project was the contrast between the initial symptomatological similarity of the patients diagnosed as schizophrenics, both within and across the centres, and the marked variation of the forms of course and outcome of the disorders over the subsequent five years. A combined index of 'overall outcome', based on the pattern of course, the total duration of the psychotic episodes, the quality of the remission (if any), and the degree of social impairment, demonstrated that, as a group, the patients in the three developing countries – Nigeria, India and Colombia – had a significantly better outcome than their counterparts in the developed countries.

Although not entirely unprecedented in reporting such findings (apart from clinical impressions and anecdotal accounts, a more favourable outcome of schizophrenic conditions in Third World communities had been described on the basis of a follow-up by Murphy & Raman, 1971), the IPSS was the first large-scale cross-cultural study using standardized assessment techniques to indicate an effect of culture on the course of schizophrenic disorders. However, the IPSS was not an epidemiological study in the strict sense and the patients selected for it could not necessarily be considered representative of the range of syndromes and conditions that might meet specified criteria for a diagnosis of schizophrenia in different cultural settings.

In view of the great potential significance of the conclusions of the IPSS, a need was felt for a more focused investigation of the frequency and 'natural history' of schizophrenia and related disorders, which would be based on more representative patient populations in different cultures. Since long-term birth cohort studies, or repeated census investigations of entire populations were hardly possible, this need could be met in two alternative ways, by selecting for study: (i) a *prevalence*-based sample or (ii) an *incidence*-based sample.

A prevalence sample, identified by the com-

Table 1.1. *Descriptive features of epidemiological surveys which have produced incidence or morbid risk data on schizophrenia*

Author and year of publication	Country	Type and size of population studied	Target group or sample investigated	Case-finding approach	Method of assessment and diagnosis	Remarks
Birth cohort studies						
Klemperer (1933)	Germany	Urban (city of Munich)	Randomly selected birth cohort 1881–1890 ($N = 1000$)	Tracing of all probands attempted (44% traced)	Personal examination or key informant (271 examined)	
Fremming (1947)	Denmark	Rural, island of Bornholm* ($N = 46000$)	Full birth cohort 1883–1887 ($N = 5500$)	Tracing of all probands (92% traced)	Personal examination	*Same population surveyed by Strömgren (1938)
Helgason, T. (1964)	Iceland	Mixed (total $N = 85183$ in 1910)	All members of the birth cohort 1895–1897 who were alive in 1910 ($N = 5400$)	Tracing of all probands (99·4% traced)	Hospital records and personal examination	
Census and longitudinal studies of whole populations						
Brugger (1931)	Germany (Thuringia)	Mixed ($N = 37561$)	All persons 'suspect' for mental disorder	Records and key informants consulted to detect 'suspects'	Personal examination of all 'suspects' and of a sample of 'healthy' persons	
Brugger (1933, 1938)	Germany (Bavaria)	Two rural areas ($N = 5425$ and 3203)	All inhabitants	Door-to-door interviewing	Personal examination (semi-structured interview)	
Strömgren (1938)	Denmark	Rural, island of Bornholm* ($N = 46000$)	All inhabitants	Key informants; door-to-door interviews in a sample area	Personal examination	*Same population studied by Fremming (1947)
Sjögren (1948); Larsson & Sjögren (1954)	Sweden	Rural, two islands off the west coast	All persons born or resident on the islands	Door-to-door interviewing, parish records	Personal examination	*Longitudinal data covering 45 years collected
Böök (1953); Böök *et al.* (1978)	Sweden	Rural* ($N = 8891$ in 1949; $N = 5748$ in 1974)	All inhabitants pedigrees	Door-to-door interviewing	Personal examination; biochemical tests on subsample in 1974–77	*Genetic isolate
Surveys based on service contacts						
Ödegaard (1946)	Norway	Whole country	All first admissions ($N = 14231$) during 1926–1935		Hospital diagnosis	
Shepherd (1957)	England	County of Buckinghamshire ($N = 400000$)	All first and readmissions for 1931–1933 and 1945–1947		Hospital diagnosis, grouped by author	
Hollingshead & Redlich (1958)	USA	New Haven, Conn. (area population $N = 174000$)	All individuals in psychiatric treatment during a 6-month period in 1960	Census of hospitals, clinics and private practitioners; review of clinical records	Diagnosis made at facility; 6–17% re-diagnosed by authors	
Norris (1959)	England	Catchment area ($N = 1661000$)	All persons admitted in 1947–1949	Tracing of records, 2-year follow-up		
Kadri (1963); Murphy (1968)	Singapore	University students	First admissions over a 5-year period	Screening of hospital records	Author's diagnosis	
Wing, L. *et al.* (1967)	England, Scotland and USA	Three catchment areas (London, Aberdeen, Baltimore)	All persons in episodes of contact on census day	Case registers	Diagnosis made at facility	
Adelstein *et al.* (1968)	England	City of Salford ($N = 150000$)	All persons in 'inception episodes' of contact	Case register	Hospital diagnosis	
Walsh (1969)	Ireland	City of Dublin ($N = 720000$)	All first admissions ($N = 1427$)		Hospital diagnosis	
Murphy & Raman (1971)	Mauritius	Total island population ($N = 600000$)	All first admissions $N = 94$) during 1956	Screening of hospital records; follow-up interviews 12 yr later	Records and personal examination of uncertain cases	
Liebermann (1974)	USSR	District of Moscow ($N = 248000$)	All onsets for period 1910–1964	Dispensary register	Records; personal examination at census	
Nielsen (1976)	Denmark	Island of Samsö ($N = 6823$)	All service contacts over 18 yr	General practitioners case register, census in 1964	Diagnosis made at facility admitting the patients	
Babigian (1980)	USA	Monroe county, NY county population ($N = 712000$)	Annual first-in-lifetime entries into psychiatric care	Psychiatric case register		

munity survey method, even if statistically representative, would include individuals differing according to previous length of illness and duration of exposure to treatment and psychosocial environmental influences. Also, a prevalence sample would miss patients who either died early after developing a psychotic illness, or migrated out of the study area. For these reasons, a decision was made in favour of incidence sampling, in the sense of identifying cases in the early stages of the illness and evaluating them as closely as possible to the point of their first contact with any service or helping agency. Such cases would then be followed up over a defined period of time.

Apart from being an attempt at replicating the IPSS findings on a more representative patient population, the implementation of such a design in a multi-culture setting was expected to contribute data necessary for estimating incidence rates of schizophrenia and related disorders and their cross-cultural variation. Knowledge in this respect is still scant, and the absence of comparable data on incidence of schizophrenia in various populations (especially those in the Third World) is an obvious gap in the epidemiology of this group of conditions. Table 1.1 summarizes the main features of the design of previous studies which have produced incidence or morbid-risk data.

In most of the earlier studies, the difficulty of developing an adequate case-finding method for a condition of low population incidence, such as schizophrenia, had been compounded by the lack of specific diagnostic criteria and of the standardized methods for collecting data on history and psychopathology. Therefore, much was to be gained from a multi-centre collaborative study in which the same methods and instruments, common diagnostic criteria, and comparable case-finding procedures, would be simultaneously applied across culturally different catchment areas. A special aim of the project was to link the epidemiological estimation of incidence rates to a diagnostic and psychopathological classification of the cases. It was explicitly recognized from the start that it would be premature to subscribe to any one of the alternative positions as to where the boundaries of schizophrenia ought to be drawn. Therefore, diagnostic concepts of varying 'width' were to be applied to the classification of cases, The subsequent validation of the diagnostic classification would take into account the psychopathological features of the conditions and a number of antecedent variables; it would be particularly strengthened by the supplementation of follow-up data.

In addition to such central epidemiological and diagnostic questions that the new study was primarily designed to tackle, there was the secondary objective of integrating into its design some recent research techniques for studying the impact of environmental factors and the prognosis of schizophrenic disorders which had not been available at the time the IPSS was planned. For example, the findings suggesting that stressful life events may precipitate an acute schizophrenic attack (Brown & Birley, 1968; Schwartz & Myers, 1977), or that living with a relative exhibiting high emotional involvement coupled with a critical or rejecting attitude increases the probability of relapse in schizophrenic patients (Brown *et al.* 1972; Leff *et al.* 1983); or that discrepancies in the way psychotic illness is perceived and interpreted by doctors and by the patient's family (Katz *et al.* 1978), could be of considerable relevance in explaining culture-related differences in the prognosis of psychotic disorders. Further refinement of the measurement of course and outcome could be achieved if the assessment instruments were designed to allow a better separation of clinical symptoms, functional impairments and social disabilities (Jablensky *et al.* 1980). Some of the results of these special studies have already been published (Day *et al.* 1987; Leff *et al.* 1987, 1990; Wig *et al.* 1987); other reports are to follow.

Chapter 1 Design and methods

The present study, which at its inception was given the title 'Determinants of Outcome of Severe Mental Disorders', was designed in 1975–6, and the first patients were assessed in August 1978. The twelve field research centres participating in the project are: Aarhus* (Denmark), Agra* and Chandigarh (India), Cali* (Colombia), Dublin (Ireland), Honolulu and Rochester (USA), Ibadan* (Nigeria), Moscow* (USSR), Nagasaki (Japan), Nottingham (United Kingdom) and Prague* (Czechoslovakia).[1] Six of these centres (indicated by an asterisk) had taken part in the IPSS. The twelve centres represented research settings of widely different and contrasting cultural and socioeconomic characteristics. Like the IPSS, the Outcome study was supported jointly by WHO, NIMH, and the twelve field research centres. The central coordination of the project was the responsibility of the WHO Headquarters in Geneva.

GENERAL DESIGN

The complex design of the Outcome study is represented schematically in Fig. 1.1. All the centres took part in the so-called 'core' study which involved prospective case-finding, clinical, diagnostic and social assessment of the cases, and follow-up re-examinations at one year and at two years after the initial examination. In addition, subgroups of several centres each carried out special exploratory studies on subsamples of the patients with the aim of investigating: (i) the role of life events in the onset of psychotic episodes; (ii) the effects of 'expressed emotion' in the family on the risk of psychotic relapse; (iii) the nature and severity of specific behavioural impairments and social disabilities; and (iv) the influence of the family members' perception of the patient's behaviour on the course of the disorder.

The present report is limited to the epidemiological aspects, the initial clinical assessment findings, and the principal follow-up results of the 'core' study; the results of the special investigations on life events, emotional interactions in the family, and family perceptions, are the subject of separate publications (Day *et al.* 1987; Wig *et al.* 1987; Leff *et al.* 1987, 1990; Katz *et al.* 1988); the data on levels of disability of the patients will be reported subsequently.

Inclusion criteria and case finding

The aim of the 'core' study was to identify and assess, in each of the 13 catchment areas[2] (see Table 1.2 for size of population), individuals who met all of the following four inclusion criteria and none of the exclusion criteria.

A. Inclusion criteria

(i) Age 15–54.

(ii) Residence of at least 6 months in the area in the year preceding the initial examination.

(iii) Evidence of presence, in the preceding 12 months, of *at least one* of the following overt psychotic symptoms: hallucinations or pseudohallucinations in any modality; delusions; qualitative thought or speech disorder; qualitative psychomotor disorder; or gross behavioural abnormalities representing a break in the person's previous pattern; *or at least two* of the following abnormalities suggestive of psychotic disorder: loss of interests, initiative and drive leading to deterioration of performance; onset of social withdrawal; episodic severe excitement, purposeless destructiveness or aggression; episodic or persistent states of overwhelming fear or anxiety; gross and persistent self-neglect.

(iv) First-in-lifetime contact with any 'helping agency' within the last three months, occasioned by the symptoms and behaviours enumerated under (iii).

[1] In the tables: AAR = Aarhus; AGR = Agra; CAL = Cali; CHA/R = Chandigarh, rural area; CHA/U = Chandigarh, urban area; DUB = Dublin: HON = Honolulu; IBA = Ibadan; MOS = Moscow; NAG = Nagasaki; NOT = Nottingham; PRA = Prague; ROC = Rochester.

[2] The Chandigarh centre investigated two catchment areas, one urban and one rural.

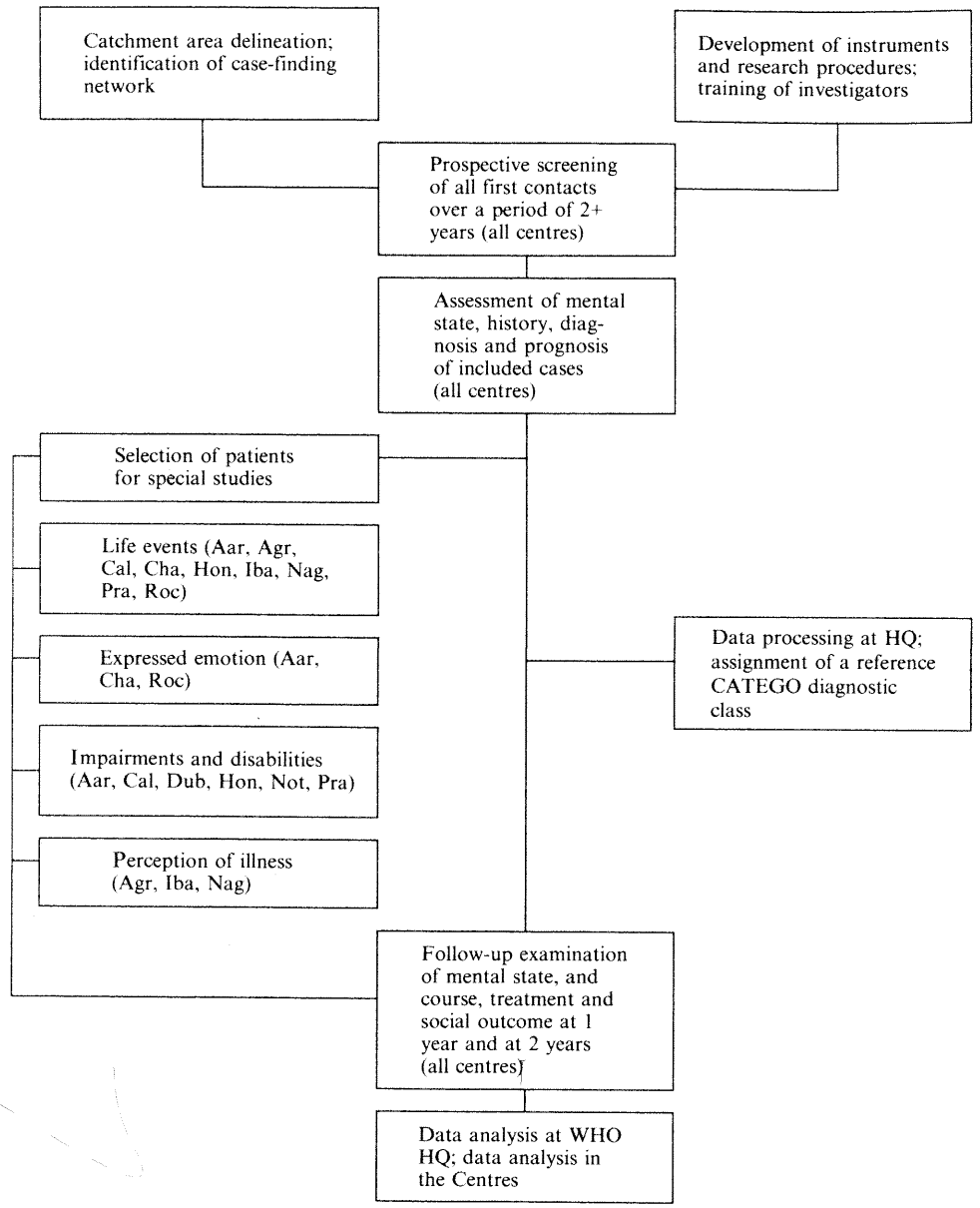

FIG. 1.1. Schematic representation of the design of the study.

B. Exclusion criteria[3]

(v) Clinical evidence of gross organic cerebral disorder, including CNS damage due to alcohol or drug abuse, and manifest in either delirium or dementia, with or without peripheral neuropathy.

(vi) Previous contact with psychiatric, other medical, or non-medical agencies, upon which a mental disorder identical or similar to the current one had been diagnosed or suspected.

The inclusion criteria were set with a view to maximizing the probability that the study population would ultimately consist of patients with either main or alternative clinical diagnoses of schizophrenia (ICD-9 categories 295.0–9); paranoid psychosis (297.0–9); reactive psychosis, paranoid and unspecified (298.3, 298.4, 298.8); unspecified psychosis (298.9); and other conditions in which an underlying schizophrenic illness could not be excluded (e.g. paranoid and schizoid personality disorders, ICD 301.0 and 301.2; or paranoid and hallucinatory illness associated with alcohol or drug use, ICD 291.3, 291.5, 292.1, without evidence of gross organic pathology). Since schizophrenia cannot be ruled out in the instance of a paranoid or hallucinatory psychosis without organic features in a person with a history of alcohol or drug use, it was decided to allow such cases to be included.

[3] Severe mental retardation and communication difficulties (e.g. deafness) were also reasons for exclusion from the Study.

Table 1.2. *Catchment area populations*

Centre	Total	Age groups 15–54
Aarhus	574000	314344
Agra	2806346	1426755
Cali	1347466	784009
Chandigarh/rural	103865	61642
Chandigarh/urban	348609	205786
Dublin	280322	149879
Honolulu	357225	210020
Ibadan	931348	635999
Moscow	392097	231866*
Nagasaki	447444	267149
Nottingham	380023	202214
Prague	1114809	578379
Rochester	397828	237223

*Age 18–54.

At the same time the inclusion criteria were designed to block or restrict to a minimum the intake of patients with primary affective disorders.

The inclusion criteria, supplemented with definitions and decision rules, were written in a Screening Schedule (SS) which served as the principal instrument in the case finding. For the rare case, in which a strong suspicion of schizophrenia was present, even if not all of the inclusion criteria were met, the SS contained a provision of inclusion on the strength of a narrative not specifying the clinician's reasons for the decision. It should be noted that the diagnosis made at the first-contact agency or the referring facility was not one of the inclusion criteria. The goal of case finding was to select individuals presenting with specified *symptoms* and *behaviour abnormalities* indicative of definite or possible schizophrenia; such cases were to be identified by the project team using the SS, regardless of any pre-existing diagnostic label.

The case finding procedure involved the establishment of a list of all services and agencies ('intercept points') in the area which were the likely sites of contact for potential study subjects (Table 1.3); the making of the necessary notification and referral arrangements; and the continuous monitoring of these 'intercept points' with screening of all contacts for at least 24 months.

After the completion of case finding, the centres were required to carry out supplementary small-scale surveys of the original network of

Table 1.3. *Types of case-finding agencies cooperating in the study, by centre*

	Aar	Agr	Cal	Cha/R	Cha/U	Dub	Hon	Iba	Mos	Nag	Not	Pra	Roc
Psychiatric hospitals, units or institutions	X	X	X		X	X	X	X	X	X	X	X	X
Psychiatric out-patient departments or centres	X	X	X	X	X	X	X		X				
General hospitals		X			X		X						X
Polyclinics or health centres					X	X			X	X			
General practitioners		X			X					X			
Private psychiatrists or physicians		X	X				X			X			
Public health nurses or social workers						X							
Rural primary health care centres				X									
Traditional healers		X		X	X			X					
Religious healers		X		X			X	X					
Police stations, prisons		X								X	X		X
Other		X	X			X	X	X					

contact sites, as well as of any other agencies which had not been included in the study, in order to search for missed cases ('leakage'). In most instances this included scanning the records of the agencies; in some centres, e.g. Aarhus and Nottingham, the search was carried out through the local psychiatric case register.

The variations in the demography, social organization and geographic characteristics of the catchment areas; the different patterns of health care and utilization of various helping agencies by the population; the unequal resources of the field research centres; and, in some instances, unanticipated events, presented constraints which necessitated certain centre-specific adjustments to be made in the case-finding protocol. In some areas the monitoring of defined contact facilities had to be supplemented by interviewing key informants in various localities (Chandigarh, Ibadan); or by limited door-to-door surveys in selected sub-units of the catchment area (Honolulu). In other centres (e.g. in Agra), the number of possible contact sites far exceeded the resources available for their monitoring; or it proved impossible to secure the full cooperation of agencies such as out-patient dispensaries, private practitioners or traditional healers (e.g. in Cali). In Rochester, unanticipated financial constraints affected the continuity of the case finding process. In Prague, an administrative re-definition of the boundaries of the catchment area of the research centre took place in the course of the first year of the study. In Ibadan, there was uncertainty about the validity of the population census data on which the estimation of the catchment area population was based.

Such obstacles made it unavoidable for several of the centres to curtail the case finding network, or modifying in other ways the case finding procedures, with a resulting uncertainty as to the completeness of coverage. At the end of the initial data collection phase, therefore, the field research centres fell into the following two groups as regards the intensity of case finding.

A. Centres which applied the case finding and assessment procedures without modification and monitored *all* known or presumed contact sites for eligible study subjects throughout the case-finding period: Aarhus, Chandigarh, Dublin, Honolulu, Moscow, Nagasaki and Nottingham.

B. Centres which found themselves compelled to introduce modifications in the original study design (e.g. excluded from monitoring some of the known or presumed contact sites; had breaks of the continuity of case finding; or employed some pre-screening selection): Agra, Cali, Ibadan, Prague and Rochester.

The modifications of the kind that occurred in centres listed under B must have affected the numbers of identified cases, although they would be of little consequence for the study of the clinical and social characteristics of the patients, including course and outcome of their disease. In order to base the estimation of the incidence of schizophrenia and related disorders on the strongest possible evidence as regards the completeness of case finding, rates are reported separately in Chapter 3 for the two groups of centres. However, material from all the centres has been used for the clinical and diagnostic analysis described in Chapter 2, and follow-up data from all the centres (except Rochester) are reported in Chapter 4.

Clinical and diagnostic assessment

The assessment of the subjects who had passed the screening stage included the following steps (the main features of the instruments used in the core component of the Outcome Study are summarized in Table 1.4).

(1) *Mental state*

Current psychopathology (symptoms occurring in the last one month and at the point of examination) was evaluated in a clinical interview, administered by a psychiatrist using the 9th edition of the Present State Examination, (PSE – Wing *et al.* 1974). For significant symptoms which fell outside the one-month limit, the examiner was required to fill in the PSE Syndrome Check List, included in the Diagnostic and Prognostic Schedule (DPS)

(2) *Past history*

A new instrument, the Psychiatric and Personal History Schedule (PPHS), was constructed specially for the study. The PPHS is a standardized guide to history data collection which can use multiple sources of information: a relative or other 'key' informant, the patient himself, clinic or hospital records, etc. The PPHS enquiry aims at a detailed reconstruction of the mode of onset and the early manifestations of the illness

Table 1.4. *Main features of the research instruments*

Instrument	General description	Source of information	User
Screening Schedule (SS)	A checklist containing 2 demographic, 4 history, 5 symptomatological, and 5 behavioural items, all dichotomous (yes/no). Definitions and guidelines included, as well as provisions for recording diagnoses. Output: decision concerning patient's eligibility for further study.	Admission records and case notes; brief personal interview with patient and/or key informant	Psychiatrist
Present State Examination (PSE), 9th edn	A guide to a semi-structured, standardized clinical interview covering symptoms present in last 4 weeks. A total of 140 mental state and behaviour items, rated for intensity and duration, divided into 20 sections. Glossary definitions of symptoms and rating rules available. Both symptom profiles and section scores obtainable. Standard syndromes and diagnostic classes can be derived by CATEGO computer program using PSE ratings as input.	Interview with the patient	Psychiatrist
Psychiatric and Personal History Schedule (PPHS)	A guide to standardized psychiatric medical, social and developmental history taking, with suggested probes and instructions for rating. Contains sections on psychiatric history (present illness and past episodes; onset; progression of symptoms; informant's and patient's own perception of problem; treatment); medical history; residence; household and family; social network; marriage; children; sexual behaviour; parents and sibs; occupation; education; religion; developmental history; and pre-morbid personality.	Interviews with key informants and patient; case notes and other written records	Social worker, psychologist or psychiatrist
Diagnostic and Prognostic Schedule (DPS)	A summary of diagnostically and prognostically important information; main, alternative and supplementary diagnosis in centre-specific terminology and in ICD terms; ratings of clinical and social prognosis for next 12 months; checklist of treatments and services with ratings of whether needed and available; checklist of PSE syndromes; narrative summary on the case.	All available data on the patient; PSE and PPHS	Psychiatrist
Follow-up Psychiatric and Personal History Schedule (FU-PPHS)	As PPHS, but items re-formulated so as to rate change. Added charts for month-to-month narrative recording and coding of symptoms, treatments, and social events	As PPHS	Preferably psychiatrist
Disability Assessment Schedule (DAS)	A rating schedule containing 97 items grouped in 4 sections: overall behaviour, social roles, behaviour in hospital and modifying factors. Performance of each social role in the last 4 weeks is rated on a 6-point scale, with anchor points for 'no dysfunction', 'minimum dysfunction', and 'maximum dysfunction'. Manual with guidelines and rating rules available.	Interview with key informant and/or patient	Social workers, psychologist or psychiatrist

(including the responses of the patient's social environment), the past medical and psychiatric history, the family background, social functioning and circumstances, and the development of the pre-morbid personality.

(3) *Diagnosis*

The diagnostic assessment of each case, made by the centre investigators, was recorded in a DPS. In seven of the centres the diagnosis was based on a consensus between two or more investigators (in Nottingham, the chief investigator reviewed all the diagnoses). In five centres the DPS was filled in by an individual investigator and no case by case review by the research team was involved.

The DPS requires: (i) a diagnosis of the current mental state (i.e. a diagnosis of the psychopathological syndrome manifest at the time of the initial examination); (ii) a 'main' diagnosis of the condition (i.e. a nosological diagnosis taking into account the previous history and all other information available); and (iii) alternatives to the main diagnosis and supplementary diagnoses of any accompanying conditions or personality disorder. The diagnostic statements could be made in the format and terminology customary in each centre, but the appropriate ICD-9 numerical codes had to be assigned to them in accordance with the ICD-9 glossary (WHO, 1978). The correctness of the assignment was verified at the study Headquarters. In the same schedule, a number of ratings were made of the psychiatrist's judgement about the prognosis of the case for the next 12 months, and of the estimated need for

Table 1.5. *Cases screened, cases included and cases missed in the data collection phase*

	Aar	Agr	Cal	Cha/R	Cha/U	Dub	Hon	Iba	Mos	Nag	Not	Pra	Roc	All
Patients who passed initial screening	128	95	157	66	198	83	80	144	198*	117	99	112	58	1535
Subsequently excluded: diagnostic reasons	26	4	2	12	43	3	10	—	—	7	5	1	2	116
Subsequently excluded: previous contacts	3	2	1	—	—	13	2	1	1	—	2	1	1	26
Subsequently excluded: outside case finding period	—	8	—	—	—	—	—	1	—	2	—	3	—	14
Final size of 2-year incidence cohort	99	81	154	54	155	67	68	142	197	108	92	107	55	1379
Possibly eligible cases missed, identified retrospectively	21	100+ (estimate)	1− (estimate)	—	1	1	1–2 (estimate)	NK	NK	5	4	257	NK	

*Collected over three years of case finding.
NK = Not known.

each of a number of checklist items of specific treatment and management measures. A detailed narrative summary of the case was also included in the DPS.

In addition to the clinical diagnostic decision made in the field research centres, there was a central diagnostic classification of the cases, using the CATEGO computer program (Wing, 1976). The program first assigns each case to one of eight graded levels (index of definition, ID), depending on whether the information recorded on the PSE is sufficient and specific enough; the CATEGO then orders the PSE material into syndromes and broader diagnostic classes in accordance with hierarchical decision making rules. Since the CATEGO version used up to date in the analysis of the project data was based on the PSE only, the resulting CATEGO classes cannot be regarded as equivalent or alternative to the clinician's diagnosis, but as its complement.

Yet another level of control of the correctness of the application of the criteria was implemented at the study Headquarters where two of the authors (A.J. and J.E.C.) independently reviewed the computerized records of all patients and jointly made decisions concerning any doubtful inclusions or exclusions.

TOTAL STUDY POPULATION

In order to increase the total number of cases available for analysis, and to reduce the effects of possible seasonal fluctuations on the detection of new cases (which might be due to an uneven propensity of people to seek help in the different seasons), or of any other random interference, the case finding was extended over two years. The total number of subjects who passed the initial screening and were given a clinical and social assessment was 1538 (Table 1.5). After the processing and checking of all the records and schedules at Headquarters for consistency with the agreed criteria for inclusion, 156 cases were excluded, the majority of them (116) for diagnostic reasons. These were cases in which neither the CATEGO assigned class was S, P, or O, nor the clinical diagnosis (main or alternative) corresponded to the ICD rubrics selected to represent a broad class of schizophrenic and related disorders. In most instances, these were patients with affective disorders who had passed the screen because of psychotic and suspected schizophreniform symptoms which later were not confirmed by the clinical examination.[4] In the remaining instances, the reasons for exclusion were either evidence of previous treatment for the current condition or a date of screening falling outside the agreed 24-month period.[5] With these additional exclusions, the final size of the study population was 1379.

[4] The case-finding procedure was over-inclusive by design, in order not to miss at that stage cases in which a schizophrenic diagnosis could not be ruled out.

[5] Case finding in Moscow was extended to 48 months, after it was discovered that full coverage of the contact sites was not achieved in the first 12 months. Incidence estimates for Moscow are based on the cases collected in the 3 years following the adjustment in the case finding procedure.

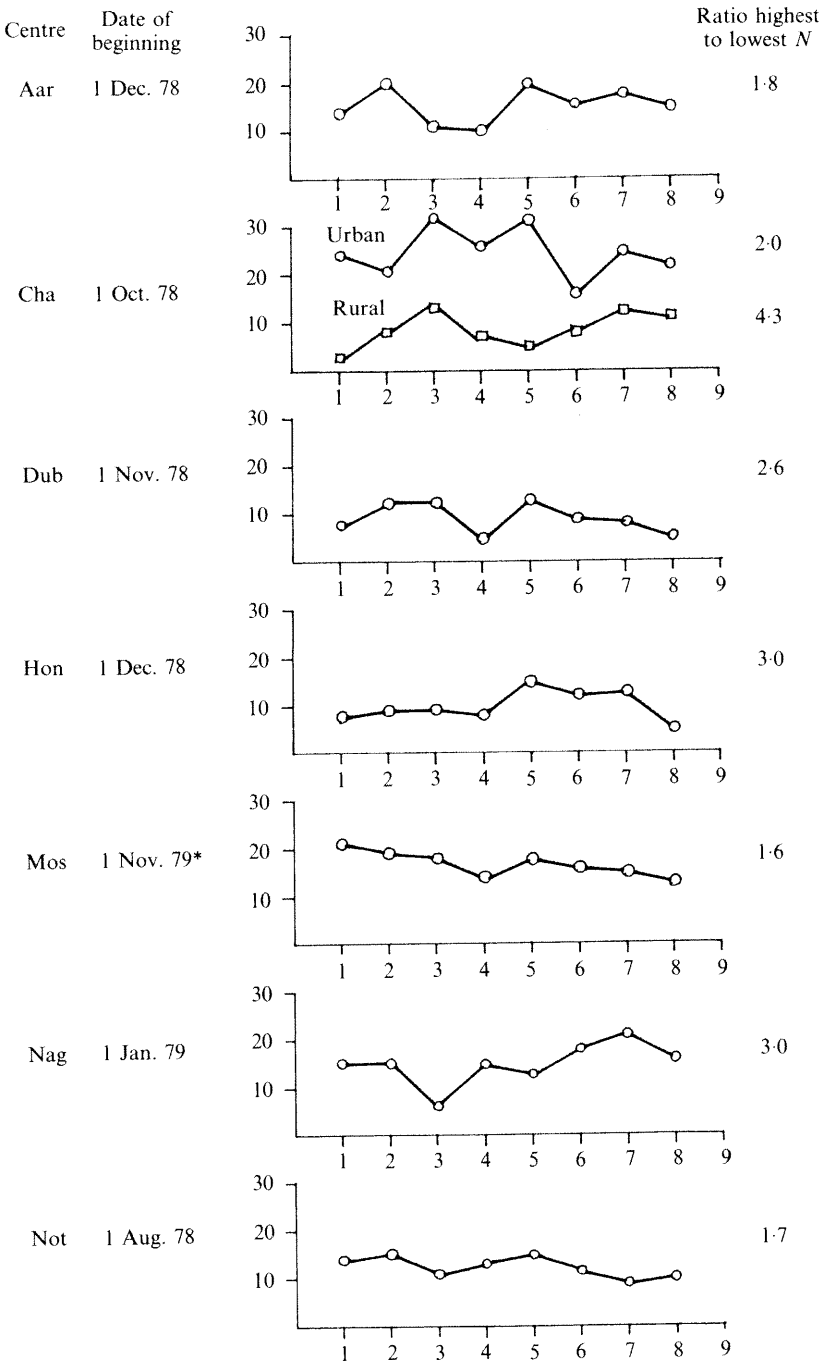

FIG. 1.2. Number of included cases by trimester (only centres with complete coverage of catchment area). (*, Excluded in the first year.)

As pointed out above, not all of the centres could achieve or maintain the full and continuous coverage of the catchment area which is required for epidemiological analysis. As expected, most of the centres which curtailed the case finding procedure later reported high numbers of potential cases which might have been included but were detected or estimated only retrospectively, through the 'leakage' studies undertaken after the completion of the prospective case finding. The retrospective search yielded small numbers of missed cases in the centres which had established a comprehensive case finding network (see the bottom line in Table 1.5).

For the latter group of centres, the number of included cases by trimester is shown on Fig. 1.2. The ratio from the highest to the lowest quarterly number of included cases, which can be taken as an index of the fluctuation of the case finding rate, did not exceed 3 (except in the rural area of Chandigarh where the population size was small).

FOLLOW-UP STUDY

All the centres participated in a follow-up of the included cases which involved the re-interviewing of patients and informants at one year and at two years following the date of the initial screening. The instruments used at such follow-up examinations included the PSE, a follow-up version of the PPHS (FU-PPHS) which allowed the recording and coding of information about symptoms, treatments and social variables on a month-by-month basis, and a modified DPS. At the second year follow-up to this package of instruments was added a Disability Assessment Schedule (DAS), designed to give a social role performance profile of each patient.

TRAINING OF INVESTIGATORS AND MONITORING OF THE RELIABILITY OF RESEARCH PROCEDURES

All the psychiatrists who participated in patient assessment in the different centres had been formally trained to use the PSE (either by one of the originators of the technique or by an experienced user). Many had extensive previous experience with the earlier version of the instrument used in the IPSS. In order to monitor inter-rater agreement on PSE assessment within those centres where more than one rater interviewed patients, the investigators were required to carry out joint interviews with every 10th patient. Agreement on PSE ratings between the centres was tested by joint rating of audio- or video-tapes during meetings of investigators. In addition, PSE audio-tapes were circulated to all the centres for rating.

The reliability of other assessments was also tested in specially designed exercises. Brief case histories were circulated to the centres and scored for the screening inclusion/exclusion criteria prior to the beginning of case finding. Similar to the PSE reliability exercise, audio-tapes of interviews using the PPHS, FU-PPHS, and DAS were supplied to the centres for training and inter-rater agreement evaluation. A synopsis of the reliability exercises is presented in Table 1.6, and the results of the analysis of the reliability data are reported below.

Table 1.6. *Number of cases assessed in intra-centre reliability exercises, by centre and research instrument*

Centre	Screening schedule	PSE	PPHS	FU-PPHS	DPS (initial)	DPS (FU)
Aar	0	16	2	2	11	0
Agr	18	34	4	13	16	17
Cal	0	8	0	1	0	5
Cha	3	29	17	0	8	0
Dub	NA	6	0	1	0	3
Hon	0	3	22	0	0	0
Iba	10	7	4	0	5	2
Mos	0	0	0	0	0	0
Nag	23	29	8	0	2	0
Not	0	7	1	6	9	0
Pra	7	9	7	0	0	0
Roc	0	0	0	0	0	0
All	61	148	63	23	51	27

NA = Not applicable.

INTRA-CENTRE RELIABILITY

(a) Screening Schedule (SS)

A total of 61 potential inclusion cases were assessed jointly by two or more investigators in 5 of the centres. Of these cases, 64% were rated as meeting the inclusion criteria and 36% as failing to meet them. Within each centre there was a perfect agreement on the inclusion/exclusion of the cases.

(b) Present State Examination (PSE)

Joint rating of cases by two investigators (alternating in the roles of an active interviewer and a passive rater) took place in all the centres except Moscow and Rochester. The number of study subjects rated in this way varied and, while four of the centres did not attain the recommended target of 10% of the patients being assessed in reliability exercises, another four centres significantly exceeded this number. The results (Table 1.7) indicate that in all the centres which provided reliability data the PSE was used at an acceptable level of inter-rater agreement, both at initial examination and at the follow-up examinations.

Table 1.7. *PSE intra-centre reliability data*

	At initial examination		At follow-up	
	Number of symptoms	%	Number of symptoms	%
(a) Symptom distribution according to levels of the intra-class correlation coefficient (ICC) (108 cases rated)				
ICC				
< 0·0	1	0·7	17	12·3
0·0–0·1	0	0·0	5	3·6
> 0·1–0·2	1	0·7	4	2·9
> 0·2–0·3	1	0·7	5	3·6
> 0·3–0·4	10	7·2	10	7·2
> 0·4–0·5	9	6·5	13	9·4
> 0·5–0·6	22	15·9	21	15·2
> 0·6–0·7	35	25·4	18	13·0
> 0·7–0·8	38	27·5	15	10·9
> 0·8–0·9	17	12·3	13	9·4
> 0·9–1·0	3	2·2	7	5·1
NV*	1	0·7	10	7·2
Total	138	100·0	138	100·0
(b) Symptom distribution according to levels of the pairwise agreement rate (PAR) (108 cases rated)				
PAR				
0·75–0·80	0	0·0	1	0·7
> 0·80–0·85	8	5·8	4	2·9
> 0·85–0·90	35	25·4	31	22·5
> 0·90–0·95	59	42·8	50	36·2
> 0·95–1·00	36	26·0	52	37·7
Total	138	100·0	138	100·0

*No variation in the ratings: ICC impossible to calculate.

The intra-class correlation coefficient (ICC) was significantly different from zero for all PSE symptoms but one (conversion), and for 137 of the 138 PSE symptoms the pairwise agreement rate (PAR) was higher than 0·80.

(c) PPHS and FU-PPHS

The data from the joint rating with the PPHS of a total of 63 cases in 8 centres indicate a high level of inter-rater agreement (PAR values higher than 0·89 and ICC values higher than 0·70) on all of the 25 history items which were selected for reliability evaluation. The follow-up version of the schedule, the FU-PPHS, was used in reliability exercises in 5 of the centres (a total of 23 cases), with similarly high levels of agreement (Table 1.8).

Table 1.8. *Intra-centre reliability (pairwise agreement rate, PAR) of selected history items assessed with PPHS and FU-PPHS*

Item	PAR
(a) PPHS (63 subjects rated)	
Type of onset	0·90
Alcohol use	0·97
Drug use	0·96
Mental illness in family	0·97
Overall adjustment in childhood	0·93
Overall adjustment in adolescence	0·89
Pre-morbid personality traits	0·94
(b) FU-PPHS (23 subjects rated)	
Remission since initial examination	0·93
Relapses since initial examination	0·94
Pattern of course	1·00
Alcohol use	1·00
Drug use	0·96
Socioeconomic level	0·86

(d) DPS

The reliability assessment of the DPS involved a determination of the diagnostic agreement on ICD-9 three-digit codes by pairs of raters, each reviewing independently all the history and mental state data collected on the subject. In the course of the initial examinations, a total of 51 cases were rated by 2 or more investigators in 6 of the centres. There were only two disagreements (one involving a diagnosis of paranoid schizophrenia *versus* paranoid state, and another involving a diagnosis of 'other' chronic organic psychosis *versus* 'other' transient organic psychosis). On follow-up, 27 cases were rated with the follow-up version of the DPS by 27 pairs of raters in 4 centres, with only one disagreement (neurotic depression *versus* reactive depressive psychosis).

The data of the intra-centre reliability exercises indicate fairly high overall levels of inter-

rater agreement in the application of the 'core' instruments of the study. However, no reliability data on any of the instruments were obtained from two of the centres, and those centres which did carry out such exercises differed according to the number of cases assessed with the different instruments. In view of the satisfactory inter-rater agreement demonstrated by all the centres which reported reliability exercise data, and the involvement of experienced clinical investigators in the two centres which did not, it would appear unlikely that the hiatuses in the intra-centre reliability data would have major implications for the validity of intra- and inter-centre comparisons.

INTER-CENTRE RELIABILITY

Inter-centre (comparing ratings done by raters from different centres) reliability exercises were carried out with the SS and the PSE.

(a) Inter-centre reliability of the SS

A total of 34 case summaries prepared by the different centres were circulated for rating as regards inclusion/exclusion, using the SS criteria. Altogether, 40 raters in all the centres except Dublin and Rochester took part in the exercise. The returns were distributed as follows: included, 63·9%; excluded, 31·5%; more information needed, 4·6%.

The mean PAR across all the 34 cases was 0·73, and the mean ICC was 0·82 (significant at $P < 0{\cdot}001$). This result can be taken as an indication that the inclusion/exclusion criteria written in the SS, which are critical to the study as a whole, were interpreted in a consistent and comparable manner by investigators responsible for the implementation of the case finding procedures in the different centres.

(b) Inter-centre reliability of the PSE

The assessment was based on the rating of 3 English-language audio-tapes of PSE interviews which were circulated to the centres. The three tapes were prepared by the Nottingham centre; the total number of raters was 16. A summary of the results is presented in Table 1.9*a* and *b*. The PAR was higher than 0·70 for 121 out of 136 PSE symptoms rated. The agreement on CATEGO syndromes was somewhat lower, due to the scoring rules which require that in both pairwise and group exercises involving more than 2 raters, a discrepant rating of a symptom is counted as a disagreement, even if in the case of a group exercise a single participant rates at variance with the majority. Assuming (arbitrarily) that PAR should be higher than 0·70 for a PSE symptom to be regarded as being reliably rated in the different centres, it can be seen (Table 1.9*b*) that only 16 out of 136 PSE symptoms did not satisfy this requirement. Of these, only 4 are included in the selective list of 44 symptoms used to construct a symptomatological profile of schizophrenia. The conclusion from the inter-centre reliability exercises using the PSE is that the instrument was applied in a sufficiently consistent and reliable manner in the centres.

Table 1.9. *PSE inter-centre reliability data (3 audiotapes rated by an average of 14 raters per case)*

(a) PSE symptom and CATEGO syndrome distribution according to levels of the pairwise agreement rate

PAR	PSE symptoms	CATEGO syndromes
0·50–0·59	4	4
0·60–0·69	13	8
0·70–0·79	22	7
0·80–0·89	39	13
0·90–1·00	60	6
Total	138	38

(b) PSE symptoms with PAR < 0·70

PSE symptoms	PAR
Worrying	0·61
Complaints of inefficient thinking	0·53
Poor concentration	0·66
Delayed sleep	0·66
*Early waking	0·64
Verbal hallucinations based on depression	0·68
*Delusional misinterpretation	0·62
*Primary delusions	0·60
*Acting out delusions	0·57
Incoherence of speech	0·63
Misleading answers	0·68
Adequacy of interview	0·65
Social impairment	0·56
Lack of self-confidence	0·68
*Delusions of persecution	0·59
Situational autonomic anxiety	0·69
*Delusions of grandiose identity	0·68

*Included in the 44-symptom profile (see Fig. 2.5).

DATA PROCESSING

Duplicates of the research schedules, or specially designed scoring sheets, were regularly mailed to Geneva throughout the data collection period. After the data had been transferred to magnetic tape, they were checked for completeness, validity and consistency. Errors were corrected by project staff, when necessary after communication with the centres concerned. Most of the computational work was carried out using standard statistical packages (SAS) but some computer programs had to be written specially for the study. Once the basic data were tabulated, the case records from each centre were again reviewed by Headquarters investigators and consultants, before proceeding with more complex statistical analyses. This process was significantly aided by the final evaluation sheets, filled in on each patient by the centre investigators. In these sheets, the research workers were asked to supplement the information contained in the schedules by providing global judgements on some items and by re-rating items which after initial scrutiny at Headquarters had been found to lack sufficient data or suffer from errors.

In addition to the statistical analyses which were performed centrally at Headquarters, most of the field research centres are analysing and reporting their own material, focusing especially on centre-specific details and issues.