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

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 100 000 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.

Chapter 4 Two-year course and outcome

The medium-term course and outcome of the disorders manifested by the original 1379 subjects who met the inclusion criteria of the project and had been assessed at the initial examination were evaluated by means of two follow-up examinations, scheduled at one year and at two years from the date of the first assessment (the date of the initial PSE was taken as the reference point).

In each research centre, the patients and, in most instances, also key informants, were invited for a follow-up interview; if no response to the letter of invitation resulted, the patients were visited at their homes. Every attempt was made to trace subjects who had changed their place of residence, and to collect at least a minimum of information on those who could not be re-interviewed. The latter represented a minority (301 out of 1379 study subjects, or an overall 'drop-out' rate of 21·8%) of the original patient series. The analysis of follow-up data reported in this chapter is, therefore, based on a total of 1078 cases (the totals in the tables which follow may not add up to this figure because of missing data on some patients in specific tabulations).

The sociodemographic and diagnostic characteristics of the patients who were not re-assessed did not deviate in any systematic manner from those of the patients who were available for follow-up. The principal characteristics of the patients who dropped out and were not re-assessed are shown in Table 4.1. There were no significant differences between patients re-assessed and patients not re-assessed on variables such as age, gender, marital status, and type of onset. Patients with reported use of street drugs were over-represented among the 'drop-outs' and the difference was significant at the 0·01 level. Considering diagnostic classification, there was no difference at the level of the 3-digit ICD-9 diagnosis, but patients falling into CATEGO classes other than S+ were more likely to be lost to the follow-up than class S+ cases ($P < 0·001$).

The 'drop-out' rate (%) showed highly significant differences ($P < 0·001$) among the

Table 4.1. *Characteristics of the patients who completed the follow-up and of those who did not*

Variable	Followed up ($N = 1078$)	Not followed up ($N = 301$)	Difference
Mean age (years)	27·9	26·6	NS
Sex (M/F)	1·1	1·3	NS
Percentage single	61·6	62·8	NS
Percentage acute onset	39·2	41·3	NS
Percentage using drugs	14·2	20·9	$P < 0·01$
Percentage CATEGO S+	55·1	44·2	$P < 0·001$
Percentage ICD 295.3[1]	28·8	28·9	NS
Percentage ICD 295.4[2]	24·1	22·8	NS

[1] Paranoid; [2] Acute schizophrenic episode.

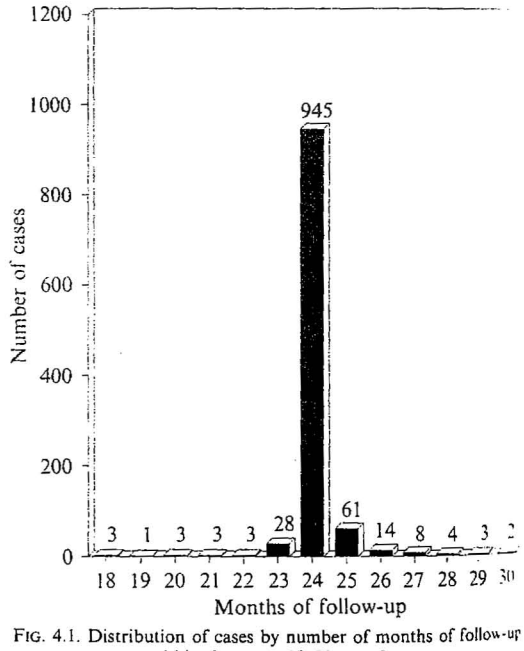

FIG. 4.1. Distribution of cases by number of months of follow-up within the range 18–30 months.

field research centres: Aarhus 19·2, Agra 6·4, Cali 9·7, Chandigarh (rural) 5·6, (urban) 30·9, Dublin 14·9, Honolulu 57·4, Ibadan 31·0,

Moscow 16·8, Nagasaki 35·2, Prague 18·7, Rochester 43·6.

The differences in the proportions of patients who were followed up were unrelated to the developing/developed country dichotomy.

The 1078 cases with a complete follow-up assessment (78·2% of the original series) provided sufficient data to enable the evaluation of the main variables describing the course and outcome of schizophrenic disorders over a period of an average length of two years following the initial examination. The actual range of the follow-up was between 18 and 30 months (i.e. it allowed for a deviation of up to 6 months either way from the target date for completion of the follow-up which had been set at 24 months after the first assessment). The distribution of cases by the completed number of months of follow-up within the permissible range of 18 to 30 months is shown on Fig. 4.1.

METHODS AND INSTRUMENTS USED ON FOLLOW-UP EXAMINATIONS

Every patient, available for a follow-up assessment, had a PSE interview. Both patient and informant provided information for the Follow-Up Psychiatric and Personal History Schedule (FU-PPHS); in many instances this information was supplemented with data from hospital or clinic notes. Apart from an updating review of the main demographic and social data about the patient, the FU-PPHS contains a month-by-month chart of symptomatology, treatment, and life events, which was designed to enable a reconstruction of the course of the condition over the preceding 12 months. Upon completion of the PSE and the FU-PPHS, the investigators were required to record their overall impressions and conclusions in the Follow-Up Diagnostic and Prognostic Schedule (FU-DPS), and to write a narrative summary of the patient's progress. An additional instrument, the WHO Disability Assessment Schedule (WHO-DAS) was also rated at follow-up examinations, and the results of the analysis of the data obtained with it will be reported in subsequent publications.

The extensive data collected on follow-up examinations were processed and tabulated at WHO Headquarters, and reviewed at a meeting of the collaborating investigators. An agreement was reached on how to aggregate the large number of variables that had been followed up, and each centre produced its own summary chart of the main course and outcome characteristics on every patient. These summary charts were coded and double-checked for consistency against the original dataset at WHO Headquarters, any discrepancies between the centres and WHO Headquarters were resolved through correspondence or discussion. The information used in the analyses presented below has, therefore, been subjected to multiple checks.

GENERAL DESCRIPTION OF THE TWO-YEAR COURSE AND OUTCOME

The following variables were assessed with a view to describing the general features of the 2-year course and outcome of the study patients: (1) pattern of course (a composite rating of the number of discrete psychotic and non-psychotic episodes observed over the follow-up period, and of the number and clinical quality of the remissions, if any); (2) proportion of the total length of the follow-up period during which the patient was in psychotic episodes; (3) proportion of the follow-up period during which the patient was in a complete remission (symptom-free); (4) proportion of the follow-up period during which the patient was on anti-psychotic medication; (5) proportion of the follow-up period during which the patient was in psychiatric hospital; and (6) proportion of the follow-up period during which the social functioning of the patient was unimpaired. Each of these variables had an operational definition, and the ratings provided by the centres were checked at Headquarters.

The results described below apply to all patients who met the original inclusion criteria and completed the follow-up, i.e. to the patients falling into the 'broad' diagnostic category of schizophrenia, which was based on the presence of either an eligible clinical (centre) diagnosis in ICD-9 terms, or a CATEGO class S, P, or O on initial examination.

Pattern of course

The categories used to classify the course of the disorder were as follows.

1, single psychotic episode followed by a complete remission;

2, single psychotic episode followed by an incomplete remission;
3, single psychotic episode followed by one or more non-psychotic episodes, with complete remissions between all or most of the episodes;
4, single psychotic episode followed by one or more non-psychotic episodes, with incomplete remissions between all or most of the episodes;
5, two or more psychotic episodes, with complete remissions between all or most of the episodes;
6, two or more psychotic episodes, with incomplete remissions between all or most of the episodes;
7, continuous psychotic illness (no remission); psychotic symptoms present most of the time;
8, continuous non-psychotic illness (no remission); psychotic symptoms may be present for some time but non-psychotic symptoms predominate throughout;
9, information inadequate for rating the pattern of course.

The distribution of the patients over these different patterns of 2-year course is shown in Table 4.2. Considering the entire series of cases with completed follow-up, the majority of the patients (50·3 %) had a single psychotic episode, i.e. fell into one of the patterns 1–4. A substantial proportion (33·1 %) had two or more psychotic episodes, i.e. pattern 5 or 6, and only a minority (14·6 %) of the patients had an unremitting, continuous psychotic illness (pattern 7). However, there was significant variation among the centres. For example, the percentages of cases with single psychotic episodes (patterns 1–3) in the course of the follow-up ranged from 27·5 in Aarhus to 75·0 in Chandigarh (rural area); those patients with two or more psychotic episodes (patterns 5 and 6) were in the range between 19·2 (Chandigarh, rural area) and 52·5 (Aarhus); and those subjects with continuous psychotic illness were in the range between 2·0 (Ibadan) and 32·9 (Nagasaki).

The individual patterns can be combined in different ways to obtain more global descriptors of the course of the disorder. A summation of the cases of patterns 1, 3 and 5 indicates that the proportion of remitting schizophrenic illnesses with complete remission is high and amounts to no less than 48·1 % of all cases. The proportion of patients with incomplete remissions is 35·3 %;

Table 4.2. *Pattern of course (all patients who were followed up), by centre (percentage distribution)*

Pattern of course	Centres in developed countries									Centres in developing countries						All centres N = 1078
	Aar N = 80	Dub N = 57	Hon N = 29	Mos N = 164	Nag N = 70	Not N = 86	Pra N = 87	Roc N = 31	All developed N = 604	Agr N = 76	Cal N = 140	Cha/R N = 50	Cha/U N = 110	Iba N = 98	All developing N = 474	
1 Single psychotic episode, complete remission	12·5	14·0	3·5	7·9	5·7	29·1	32·2	19·4	15·5	54·0	24·3	42·0	27·3	51·0	37·0	25·1
2 Single psychotic episode, incomplete remission	13·8	17·5	17·2	24·4	21·4	10·5	10·3	19·4	17·2	...	22·9	10·0	12·7	4·1	11·6	14·8
3 Single psychotic episode, non-psychotic episodes complete remission	1·2	8·8	13·8	4·9	2·9	8·1	11·5	3·2	6·6	4·0	2·1	16·0	10·9	5·1	7·6	6·4
4 Single psychotic episode non-psychotic episodes, incomplete remission	...	5·3		13·4			5·5	6·5	5·2	...	2·1	8·0	2·7	1·0	2·3	4·0
5 2+ psychotic episodes, complete remission	13·8	14·0	6·9	5·5	20·0	23·3	23·0	16·1	14·8	19·7	18·6	8·0	18·2	25·6	19·1	16·6
6 2+ psychotic episodes incomplete remission	38·7	24·7	20·7	24·4	17·1	10·5	9·2	25·8	20·9	4·0	12·1	10·0	13·6	10·2	10·5	16·5
7 Continuous psychotic illness, no remission	20·0	13·3	27·6	14·6	32·9	18·6	6·9	9·7	17·4	18·4	17·1	4·0	10·0	2·0	11·1	14·5
8 Continuous non-psychotic illness									2·4				4·6		1·1	1·8
9 Not known																

Table 4.3.

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Table 4.3. *Distribution of cases by percentage of follow-up spent in psychotic episodes*

Centre	No. of patients	Percentage of time in psychotic episodes 1–5	6–15	16–45	46–75	76–100	Total
Aar	80	26·3	17·5	27·5	7·5	21·3	100·1
Dub	57	14·0	50·9	19·3	1·8	14·0	100·0
Hon	29	34·5	20·7	13·8	—	31·0	100·0
Mos	164	17·7	31·7	24·4	7·3	18·9	100·0
Nag	69	4·4	18·8	30·4	11·6	34·8	100·0
Not	86	24·4	25·6	19·8	7·0	23·3	100·1
Pra	87	17·2	47·1	25·3	2·3	8·1	100·0
Roc	31	32·3	35·5	22·6	—	9·7	100·1
Agr	76	23·7	34·2	17·1	4·0	21·2	100·2
Cal	139	6·5	26·6	22·3	17·3	27·3	100·0
Cha/R	49	27·5	35·3	27·5	3·9	5·9	100·1
Cha/U	107	23·4	37·4	21·5	6·5	11·2	100·0
Iba	96	20·8	53·1	19·8	4·2	2·1	100·0
All	1070	18·8	33·6	22·7	7·0	17·9	100·0

and that of cases with unremitting psychotic symptoms is 14·5%.

Proportion of the follow-up period spent in psychotic episodes

The proportions of the cases which fall into the different percentiles of the total follow-up time spent in psychotic episodes (obtained by summing up the duration of all discrete episodes) are presented in Table 4.3. Nearly identical proportions (18·8% and 17·9%) of patients fall into the extremes of very short (up to 5% of the length of the follow-up period) and very long (76–100% of the period) total duration of the psychotic episodes. Within these two extreme categories, there is marked variation in the share of each field research centre. Thus, the proportions of patients who spent in psychotic episodes less than 5% of the follow-up period vary from 4·4% in Nagasaki to 34·5% in Honolulu. Higher proportions (over 20%) were observed in all of the centres in developing countries except Cali, and also in three of the centres in developed countries (Aarhus, Honolulu and Nottingham). As regards the subjects who spent 76–100% of the time in psychotic episodes, their proportions range from 2·1% in Ibadan to 34·8% in Nagasaki; these proportions generally tend to be higher in the centres in developed countries (except for Dublin and Prague) but they are similarly high in two of the centres in developing countries (Agra and Cali).

Proportion of the follow-up period in complete remission

The percentage of time during which patients are symptom-free is not simply the reciprocal value of the percentage of time spent in psychotic episodes because a certain number of subjects had non-psychotic episodes or incomplete remissions, in addition to having been psychotic for some of the time. However, there is a fair correspondence between the distributions of cases over 'time psychotic' and 'time in complete remission' (Table 4.4).

Overall, 29·4% of the patients were symptom-free (complete remission for 76–100% of the time; on the other hand, 42·9% never attained a complete remission during the follow-up. The proportion of cases in complete remission over 46–100% of the follow-up period is 44·6%.

The extremes of the distributions by centre are illustrated by Nagasaki and Ibadan where 7·3% and 73·1% respectively of the patients fell within the range of 76–100% symptom-free time, and by Ibadan and Moscow, with 7·5% and 77·4% respectively of the patients not having had any symptom-free interval during the follow-up.

Proportion of time on antipsychotic medication

This measure of the course of psychotic disorders is based on a month-by-month review of the treatment chart contained in the FU-PPHS in which every prescribed medication was recorded; the study design did not envisage

Table 4.4. *Distribution of cases by percentage of the follow-up period spent in complete remission*

Centre	No. of patients	Percentage of time spent in complete remission						Total
		0	1–5	6–15	16–45	46–75	76–100	
Aar	80	70·0	—	—	1·3	11·3	17·5	100·1
Dub	56	55·4	—	—	10·7	12·5	21·4	100·0
Hon	28	57·1	3·6	3·6	7·1	14·3	14·3	100·0
Mos	164	77·4	1·2	1·2	1·2	4·3	14·6	99·9
Nag	69	65·2	—	2·9	10·1	15·5	7·3	100·0
Not	86	30·3	—	3·5	10·5	16·3	39·5	100·1
Pra	87	29·9	—	—	9·2	21·8	39·1	100·0
Roc	31	54·8	—	—	12·9	3·2	29·0	99·9
Agr	76	21·1	1·3	2·6	1·3	10·5	63·2	100·0
Cal	138	37·0	0·7	5·8	24·6	21·7	10·1	99·9
Cha/R	50	28·0	—	2·0	8·0	32·0	30·0	100·0
Cha/U	108	23·2	0·9	6·5	14·8	25·0	29·6	100·0
Iba	93	7·5	2·2	—	6·5	10·8	73·1	100·1
All	1066	42·9	0·8	2·5	9·4	15·2	29·4	100·2

Table 4.5. *Distribution of cases by percentage time of the follow-up during which the patients were prescribed antipsychotic medication*

Centre	No. of patients	Percentage of time on psychotic medication						Total
		0	1–5	6–15	16–45	46–75	76–100	
Aar	80	3·8	—	6·3	16·3	23·8	50·0	100·2
Dub	56	5·4	1·8	8·9	8·9	19·6	55·4	100·0
Hon	29	6·9	10·3	20·7	24·1	3·5	34·5	100·0
Mos	164	—	0·6	3·7	3·7	4·3	87·8	100·1
Nag	70	2·9	—	4·3	10·0	17·1	65·7	100·0
Not	84	3·6	9·5	10·7	25·0	13·1	36·9	99·8
Pra	86	1·1	2·3	8·0	14·8	21·6	52·3	100·1
Roc	31	6·5	6·5	22·6	12·9	25·8	25·8	100·1
Agr	76	4·0	32·9	32·9	22·4	5·3	2·6	100·1
Cal	139	3·6	9·4	18·0	36·0	23·0	10·1	100·1
Cha/R	49	8·2	14·3	28·6	26·5	18·4	4·1	100·1
Cha/U	109	13·8	7·3	15·6	20·2	24·8	16·5	100·2
Iba	96	—	4·2	11·5	19·8	25·0	40·6	100·1
All	1069	3·9	6·9	13·1	18·3	17·1	40·6	99·9

plasma level monitoring or determination of metabolite excretion in the urine. Therefore, the actual extent of compliance with the prescribed medication was not known. Nonetheless, this variable is informative as a measure of the estimated need for pharmacological treatment and maintenance which, in turn, reflects the psychiatrist's perception of the severity of the course of the illness. However, the variable also reflects different treatment practices in different locations.

The data (Table 4.5) show a considerable variation among the centres in this respect. There is a marked tendency within the centres in developed countries to maintain patients on antipsychotic medication for much longer periods of time, as compared to centres in developing countries. Between 34·5% (Honolulu) and 87·8% (Moscow) of the patients in the developed countries were prescribed neuroleptics for 76–100% of the follow-up period. In the developing countries, the corresponding proportions were in the range between 2·6% (Agra) and 16·5% (Chandigarh, urban area), with the exception of Ibadan where a relatively high proportion (40·6%) were prescribed neuroleptic treatment for 76–100% of the time. However, since compliance was not monitored, and the impression of the Ibadan investigators was that few patients actually adhered to the treatment as

Table 4.6. *Distribution of cases per percentage time of the follow-up spent in a psychiatric hospital*

Centre	No. of patients	Percentage of time in psychiatric hospital						Total
		0	1–5	6–15	16–45	46–75	76–100	
Aar	80	5·0	28·8	28.8	25·0	8·8	3·8	100·2
Dub	57	15·8	21·1	43·8	14·0	3·5	1·8	100·0
Hon	29	6·9	65·5	13·8	13·8	—	—	100.0
Mos	164	1·8	13·4	47·6	34·8	1·8	0·6	100·0
Nag	70	28·6	4·3	22·8	25·7	7·1	11·4	99·9
Not	86	10·5	27·7	38·4	20·9	3·5	—	100·0
Pra	87	—	5·8	40·2	47·1	6·9	—	100·0
Roc	31	—	32·2	54·8	6·5	3·2	3·2	99·9
Agr	76	73·7	11·8	5·3	5·3	2·6	1·3	100·0
Cal	139	23·7	46·8	27·3	2·2	—	—	100·0
Cha/R	45	91·1	6·7	2·2	—	—	—	100·0
Cha/U	109	80·7	11·0	6·4	1·8	—	—	99·9
Iba	97	69·1	10·3	17·5	3·1	—	—	100·0
All	1070	31·0	20·2	27·9	16·8	2·7	1·4	100·0

prescribed, it is highly unlikely that the good outcome of the majority of the cases in that centre was in any way related to a high medication rate.

On the other hand, very few patients in any centre had been considered in no need of neuroleptic treatment (3·9% of the total study population). The percentage ranged from 0% in Moscow to 13·8% in Chandigarh (rural area). All in all, 40·6% of the subjects in the study were presumed to be on anti-psychotic drug treatment continuously, i.e. 76–100% of the length of the follow-up period.

Proportion of time spent in psychiatric hospital

In contrast to anti-psychotic medication, the total length of time during which a patient is admitted to hospital can be determined with accuracy. Although the probability of occurrence and the length of an hospital admission may be influenced by the availability of beds and by the pressure of the local caseload, none of the centres participating in the study reported any serious difficulties in admitting project patients when necessary. It can be assumed, therefore, that in most of the centres, in both developed countries and developing countries, the proportion of time during which patients were in hospital was related to the severity of symptoms and the degree of social dysfunction.

The data (Table 4.6) indicate that, in the majority of the study centres, very few patients with a diagnosis of schizophrenia are maintained continuously in hospital. In the total sample, there were only 1·4% who spent between 76% and 100% of the follow-up period in hospital, and there was no centre, except Nagasaki, where this percentage exceeded 3·8. Not a single case in the developing countries had been continuously in hospital throughout the follow-up period. Although 69% of the study patients were admitted at some point to hospital, 48·1 remained there for less than 15% of the follow-up period (20·2% were hospitalized for less than 5% of the time). It should be noted that nearly one-third (31·0%) of the patients had never been admitted to hospital. Across the centres, however, this percentage varied from 0% in Prague to 91·1% in Chandigarh (rural area).

The highest percentages of patients with no hospital admissions during the follow-up were, apart from rural Chandigarh, in the urban area of Chandigarh (80·7%) and in Agra (73·7%). Higher rates of hospitalization occurred in several of the centres in developed countries, e.g. Nagasaki and Aarhus, which had the highest proportions of patients treated in hospital for 46–100% of the period (18·5% and 12·6% respectively), whereas Prague and Moscow had the highest proportions (87·3% and 82·4% respectively) of patients hospitalized for 6–45% of the follow-up period.

Unimpaired social functioning as a proportion of the follow-up period

This variable was assessed on the basis of all available information (recorded in the FU-PPHS) from the patient, key informants, and

Table 4.7. *Distribution of cases by percentage of the follow-up time during which social functioning was unimpaired*

Centre	No. of patients	Percentage of time of unimpaired social functioning						
		0	1–5	6–15	16–45	46–75	76–100	Total
Aar	80	35·0	—	8·8	10·0	15·0	31·3	100·1
Dub	56	51·8	—	1·8	14·3	8·9	23·2	100·[illegible]
Hon	28	53·6	7·1	7·1	3·6	14·3	14·3	99·[illegible]
Mos	164	58·5	0·6	—	3·1	12·2	25·6	99·[illegible]
Nag[1]	0	—	—	—	—	—	—	
Not	86	30·2	—	3·5	5·8	18·6	40·7	99·[illegible]
Pra	87	17·2	—	1·1	11·5	25·3	44·8	99·[illegible]
Roc	31	58·1	—	—	12·9	6·5	22·6	100·[illegible]
Agr	76	21·1	1·3	2·6	1·3	7·9	65·8	100·[illegible]
Cal	138	12·3	2·2	8·7	28·3	26·8	21·7	100·[illegible]
Cha/R	50	9·6	—	3·9	13·5	26·9	46·2	100·[illegible]
Cha/U	108	25·0	—	6·5	13·0	23·2	32·4	100·[illegible]
Iba	96	9·4	—	2·1	7·3	15·6	65·6	100·[illegible]
All	1000	30·1	0·7	3·9	10·9	17·7	36·7	100·[illegible]

[1] This item was not rated in the Nagasaki Centre.

any other relevant sources. Social functioning was considered to be unimpaired if, in the judgement of the rater, the patient's overall performance of social and occupational roles was commensurate with that expected of an 'average' person of the same age, sex, social and educational background, and culture.

Of all patients who completed the follow-up, 36·7% were rated as unimpaired in their social functioning for 76–100% of the entire period; a nearly identical proportion (30·1%) were in some degree impaired throughout the follow-up period (Table 4.7).

The proportions of patients who were unimpaired for 76–100% of the time ranged from 14·3% in Honolulu to 65·8% in Agra. At the other extreme, the percentages of subjects who were socially impaired during the entire period of the follow-up, varied between 9·4 in Ibadan and 58·5 in Moscow.

Sex differences in course and outcome

There were surprisingly few sex-related differences in course and outcome when data from centres in developed and developing countries were aggregated. When considered separately for centres in developed and developing countries, some suggestions of gender differences appeared, e.g. as regards the pattern of course, there was an excess of female subjects falling into pattern 1 (single psychotic episode, followed by a complete remission), in both developed and developing countries (Table 4.8). In the developing countries, there was a relative predominance of males in pattern of course 6 (two or more psychotic episodes with incomplete remissions between most of them), while in the developed countries males were over-represented in pattern 7 (continuous psychotic illness). On the remaining variables, such as percentage of the follow-up period spent in psychotic episodes, percentage time in complete remission, percentage time on antipsychotic medication, percentage time in hospital treatment, and percentage time of unimpaired social functioning, there were virtually no differences between the sexes (Table 4.9) when location was not considered.

Thus, it could be said that there was an over-representation of females in the most favourable pattern of course, and an over-representation of males in the two least favourable patterns, but that on the whole the course of schizophrenia, when analysed from the point of view of individual variables (i.e. not controlling for location), exhibited few consistent associations with the gender of the patient. This conclusion, however, needs to be qualified in the light of findings from the multivariate analysis of predictors of course and outcome, reported below. Sex did emerge as a predictor, but the magnitude of the effect was not of an order that would justify regarding it as a key prognostic factor.

Table 4.8 A. *Pattern of course by sex (percentage distribution): centres in developed countries*

	Aar		Dub		Hon		Mos		Nag		Not		Pra		Roc		All developed countries		
Pattern of course[1]	M $N=47$	F $N=33$	M $N=30$	F $N=27$	M $N=21$	F $N=8$	M $N=61$	F $N=103$	M $N=36$	F $N=34$	M $N=56$	F $N=30$	M $N=28$	F $N=59$	M $N=16$	F $N=15$	M $N=295$	F $N=309$	Both M+F $N=604$
1	6·4	21·2	13·3	14·8	4·8	—	9·8	6·8	8·3	2·9	26·8	33·3	17·9	39·0	12·5	26·7	13·2	18·2	15·7
2	14·9	12·1	13·3	22·2	19·0	12·5	29·5	21·4	27·8	14·7	10·7	10·0	14·3	8·5	12·5	26·7	18·6	26·2	17·4
3	2·1	—	6·7	11·1	9·5	25·0	1·6	6·8	2·8	2·9	8·9	6·7	10·7	11·9	6·3	—	5·4	7·1	6·2
4	—	—	3·3	7·4	—	—	8·2	16·5	—	—	—	—	3·6	6·8	12·5	—	3·1	7·4	5·3
5	14·9	12·1	20·0	7·4	9·5	—	3·3	6·8	13·9	26·5	25·0	20·0	32·1	18·6	12·5	20·0	15·9	13·6	14·7
6	38·3	39·4	23·3	25·9	19·0	25·0	19·7	27·2	11·1	23·5	10·7	10·0	10·7	8·5	25·0	26·7	19·7	22·7	21·2
7	23·4	15·2	16·7	7·4	28·6	25·0	24·6	8·7	36·1	29·4	17·9	20·0	7·1	6·8	18·8	—	23·0	12·3	17·1
8	—	—	3·3	3·7	9·5	12·5	3·3	5·8	—	—	—	—	3·6	—	—	—	2·0	2·6	2·3
9	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Total	100·0	100·0	100·0	100·0	100·0	100·0	100·0	100·0	100·0	100·0	100·0	100·0	100·0	100·0	100·0	100·0	100·0	100·0	100·0

[1] See Table 4.2 for definition of numbered patterns.

Table 4.8 B. *Pattern of course by sex (percentage distribution): centres in developing countries*

	Agr		Cal		Cha/R		Cha/U		Iba		All developing countries		
Pattern of course[1]	M $N=49$	F $N=27$	M $N=90$	F $N=50$	M $N=25$	F $N=25$	M $N=60$	F $N=50$	M $N=55$	F $N=43$	M $N=279$	F $N=195$	Both M+F $N=474$
1	55·1	48·1	20·0	32·0	48·0	36·0	18·3	38·0	43·6	60·5	33·3	42·6	37·1
2	—	—	24·4	20·0	8·0	12·0	13·3	12·0	5·5	2·3	12·5	10·3	11·6
3	4·1	3·7	—	6·0	4·0	28·0	8·3	14·0	5·5	4·7	3·9	10·3	6·5
4	—	—	1·1	4·0	8·0	8·0	5·0	—	—	2·3	2·1	2·6	2·3
5	18·4	22·2	18·9	18·0	4·0	12·0	16·7	20·0	25·5	25·6	18·3	20·0	19·0
6	6·1	—	14·4	8·0	20·0	—	18·3	8·0	16·4	2·3	14·7	4·6	10·6
7	14·3	25·9	20·0	12·0	4·0	4·0	11·7	8·0	1·8	2·3	12·2	9·7	11·2
8	—	—	—	—	—	—	8·3	—	—	—	1·8	—	1·1
9	—	—	1·1	—	4·0	—	—	—	1·8	—	1·1	—	0·6
Total	100·0	100·0	100·0	100·0	100·0	100·0	100·0	100·0	100·0	100·0	100·0	100·0	100·0

[1] See Table 4.2 for definition of numbered patterns.

Table 4.9. *Distribution of selected course variables (percentages) by sex: all patients with a follow-up, all centres*

Course variables		Percentage of the follow-up period						
		0	1–5	6–15	16–45	46–75	76–100	Total
Percentage time in psychotic episodes	M(N = 610)	—	20·3	32·1	21·0	7·9	18·7	100·0
	F(N = 514)	—	18·9	36·4	22·0	5·4	17·3	100·0
	M+F(N = 1124)	—	19·7	34·1	21·4	6·8	18·1	100·0
Percentage time in complete remission	M(N = 609)	44·2	0·3	3·4	10·0	13·8	28·2	100·0
	F(N = 511)	40·7	1·2	1·0	9·8	17·8	29·5	100·0
	M+F(N = 1120)	42·6	0·7	2·8	9·9	15·6	28·8	100·0
Percentage time on antipsychotic medication	M(N = 610)	4·1	7·0	13·1	16·8	19·9	39·2	100·0
	F(N = 514)	6·1	7·4	12·7	20·4	14·9	38·6	100·0
	M+F(N = 1124)	5·0	7·2	12·9	18·4	17·6	38·9	100·0
Percentage time in hospital treatment	M(N = 610)	30·3	21·0	28·5	15·1	3·3	1·8	100·0
	F(N = 513)	34·6	19·8	25·2	17·3	2·7	0·4	100·0
	M+F(N = 1125)	32·3	20·4	27·0	16·1	3·0	1·2	100·0
Percentage time of unimpaired social functioning	M(N = 571)	30·5	0·4	5·8	11·7	16·8	34·8	100·0
	F(N = 475)	28·8	1·0	1·2	11·4	18·9	38·5	100·0
	M+F(N = 1046)	29·7	0·7	3·7	11·6	17·8	36·5	100·0

Differences between developing countries and developed countries

The examination of the follow-up results for such differences was an important task, considering the findings of the IPSS which indicated, for the first time on a large scale and with the use of standardized methods, that the course and outcome of disorders diagnosed as schizophrenic were more favourable in the developing countries than in the developed countries. In view of the importance of replicating these findings, this issue was addressed in the Outcome Study on a larger and more representative series of patients, and with more refined methods. The principal results in this respect, from the point of view of simple univariate analysis, are presented on Table 4.10 which shows proportions of patients who had met the inclusion criteria and during the follow-up fell into the extreme ends of the distributions of the six major variables describing course and outcome.

As regards the 'best possible' outcomes, in five out of six comparisons, the proportions of patients in the centres in developing countries falling into these categories are considerably higher than the proportions of patients in the centres in developed countries. For example, the percentage of patients in the developing countries who exhibited a remitting course over the two years of the follow-up (i.e. patterns 1, 3 and 5), was 62·8, as compared with 36·9 in the developed countries. The percentage of patients who were symptom-free (in complete remission) for over three-quarters of the length of the follow-up period was 38·3 in the developing countries and 22·3 in the developed countries. Similarly, the percentage of patients in developing countries who functioned without

Table 4.10. *Percentage of patients in the developing countries and in the developed countries falling into selected categories of course and outcome variables*

Course and outcome category	Developing countries	Developed countries
1 Remitting course with full remission (1+3+5)	62·7	36·9
Continuous or episodic psychotic illness, without full remission (2+4+6+7)	35·7	60·9
2 In psychotic episodes 1–5% of FU period	18·4	15·1
In psychotic episodes 76–100% of FU period	15·1	29·2
3 In complete remission 0% of FU period	24·1	47·2
In complete remission 76–100% of FU period	38·3	22·3
4 No antipsychotic medication throughout FU	5·9	2·1
On antipsychotic medication 76–100% of FU period	15·9	39·9
5 Never hospitalized	55·5	5·1
Hospitalized for 76–100% of FU period	0·3	4·3
6 Impaired social functioning throughout FU	15·7	41·1
Unimpaired social functioning for 76–100% of FU period	42·9	21·2

Table 4.11. *Pattern of course by initial diagnostic classification of the cases (percentage distribution)*

Diagnostic classification on initial examination	Pattern of course									Total	*N*
	1	2	3	4	5	6	7	8	9		
CATEGO class S+	24·0	16·9	6·4	4·0	15·0	16·1	15·7	1·7	0·2	100·0	626
CATEGO classes S, P, O+	24·3	16·2	6·8	4·2	15·4	15·9	15·0	2·1	0·1	100·0	859
CATEGO classes S, P, O	24·9	15·4	7·1	4·3	15·6	15·8	14·5	2·2	0·2	100·0	968
Clinical ICD-9 diagnosis *or* CATEGO classes S, P, O	25·4	15·3	7·1	4·0	15·8	16·0	14·1	2·0	0·3	100·0	1134

1, Single psychotic episode, complete remission; 2, Single psychotic episode, incomplete remission; 3, Single psychotic episode one or more non-psychotic episodes, complete remissions; 4, Single psychotic episode, one or more non-psychotic episodes, incomplete remission; 5, 2+ psychotic episodes, complete remissions; 6, 2+ psychotic episodes, incomplete remissions; 7, Continuous psychotic illness; 8, Continuous non-psychotic illness; 9, Missing data.

impairment for 76–100% of the time was 42·9, compared with 31·6 in the developed countries. The only category for which no difference was found between developing and developed countries was that of the proportion of cases with relatively brief psychotic illnesses, i.e. with a total length of time in psychotic episodes less than 5% of the follow-up period (18·4 in the developing countries and 18·7% in the developed countries).

In the range of categories characterizing the 'worst possible' outcome, the proportions of patients in the centres in developed countries were consistently higher than the corresponding proportions of patients in the centres in developing countries: 38·3% compared to 21·6% as regards cases with continuous or episodic psychotic illness without complete remission; 41·6% compared to 15·7% as regards presence of impaired social functioning throughout the follow-up; and 20·2% compared to 15·1% as regards being in psychotic episodes for 76–100% of the length of the follow-up.

Comparisons on a centre by centre basis, as regards various course and outcome variables, are generally consistent with the overall trend outlined above. Such comparisons, however, are best considered in the context of other issues and the relevant data are presented in the remaining sections of this chapter.

DIAGNOSIS AND SUBSEQUENT COURSE AND OUTCOME

An important question concerns the extent to which 'caseness' for schizophrenia as defined by each one of the four diagnostic definitions of schizophrenia identified different two-year patterns of course and outcome. The four levels of diagnostic definition were: (i) clinical ICD-9 diagnosis of schizophrenia or of a specified related disorder, or CATEGO class S, P, or O; (ii) CATEGO classes S, P, or O; (iii) CATEGO classes S, P, or O+; and (iv) CATEGO class S+. It has been shown that each one of these four alternative diagnostic definitions, and especially (i) and (iv), was related to a different level of severity of the florid or 'positive' psychotic symptoms of schizophrenia. If diagnosis-related differences in the course and outcome of the disorders could likewise be demonstrated, the hypothesis that the diagnostic classification of schizophrenia possesses predictive validity would receive considerable support.

Diagnostic inclusion criteria and course and outcome

Table 4.11 provides a clear answer to this question: there are virtually no differences between the percentage distributions over the different categories of the variable pattern of course between the patients series meeting each one of the four sets of inclusion criteria of 'caseness'. The 'restrictive' definition of schizophrenia based on CATEGO S+ on initial examination does not select cases that are in any way different, as regards pattern of course, from the cases identified by the 'broad' diagnostic category based on either a clinical ICD-9 diagnosis or on a CATEGO class S, P, or O. Put in a different way, this finding suggests that the pattern of course is unrelated to the degree of symptomatological specificity of the inclusion criteria for schizophrenia adopted in this study.

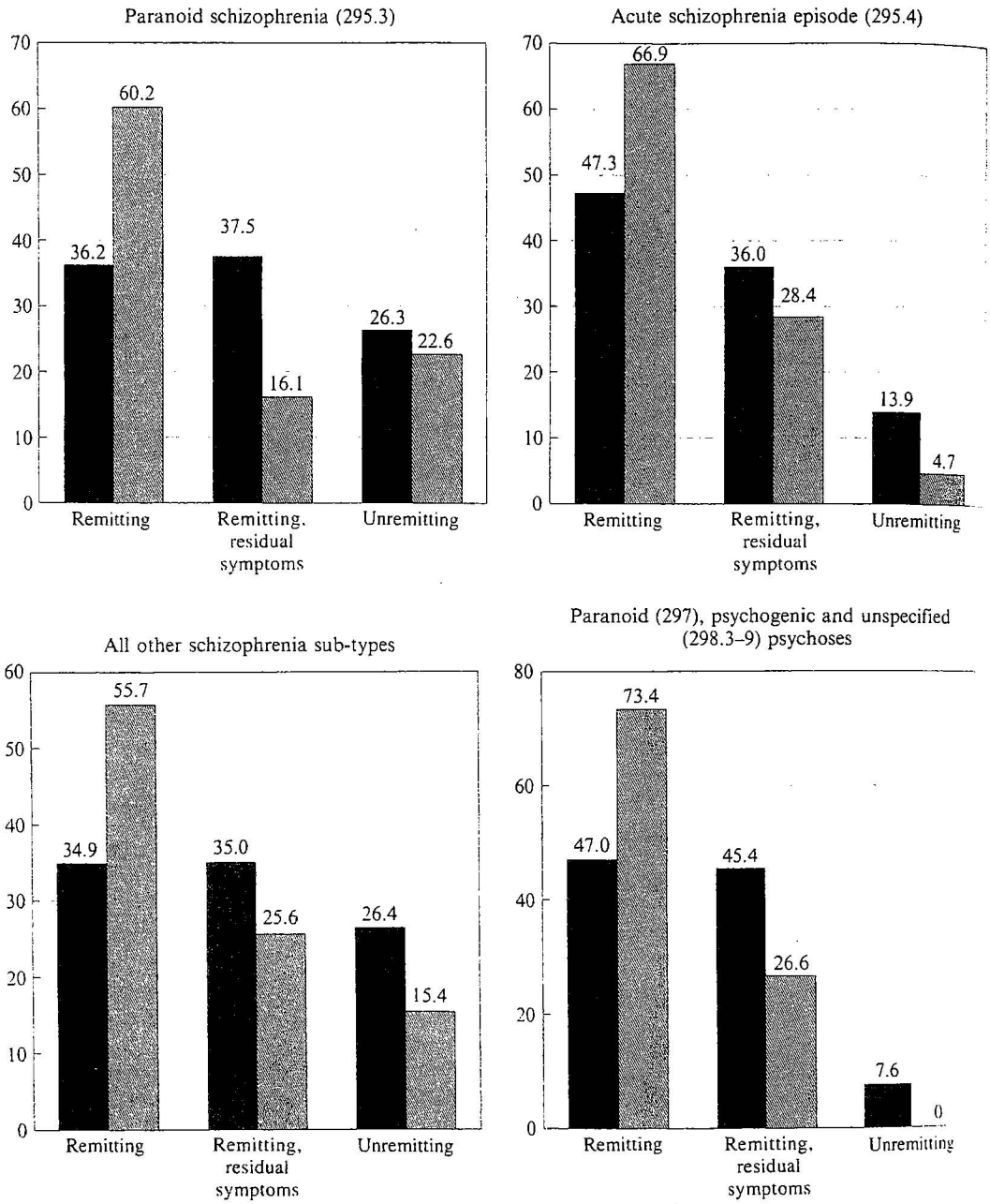

FIG. 4.2.1. Pattern of course (all patients with a follow-up) by clinical diagnosis made at field research centre on initial examination. Remitting: patterns 1, 3 and 5; Remitting, residual symptoms: patterns 2, 4 and 6; Unremitting: pattern 7. In Figs 4.2.1-4.2.5 ■ indicates 'developed countries', ▨ 'developing countries'.

Course and outcome according to clinical diagnostic subtype

The next question to be considered is whether the different clinical diagnoses, made by the psychiatrists in the field research centres on the basis of the initial examination PSE, previous history, and any other data, bear any prognostic implications. For the purposes of this analysis all diagnostic assessments made on initial exam-

Table 4.13. *Types of 'strings' of CATEGO classes occurring in the follow-up study*

Code number	Combination of CATEGO classes observed on the three examinations	*N*	%
10	S, P or O on each of the three occasions, *or* S, P or O on any two occasions and missing PSE on remaining occasion	365	35·2
9	S, P or O on any two occasions; on the remaining one occasion: A, B, X, NO	119	11·5
8·1	S, P or O on one occasion; on the remaining two occasions: either missing PSE data, or A, B, X, or NO *and* missing PSE data	140	13·5
8	S, P or O on one occasion; on the remaining two occasions: either twice A or B, or twice X or NO, or A, B and X, NO	168	16·2
7	S, P or O on one occasion and M on another occasion, with missing PSE data on the remaining one occasion; *or* S, P or O on two occasions and M on the remaining one occasion	28	2·7
6	S, P or O on one occasion and D, R or N on another occasion, with missing PSE data on the remaining one occasion; *or* S, P or O on two occasions and D, R or N on the remaining one occasion	89	8·6
5	S, P or O on one occasion and M on both remaining occasions; *or* S, P or O on one occasion, M on another occasion, and either D, R, N or A, B, X, NO on the remaining one occasion	28	2·7
4	S, P or O on one occasion, D, R, or N on another occasion, and either D, R, N or A, B, X, NO on the remaining one occasion	43	4·1
3	M on one occasion, either M or D, R, N or A, B, X, NO on another occasion, and missing PSE data on the remaining one occasion; *or* M on at least one occasion, and any combination of M, D, R, N, A, B, X, NO on one or two occasions	22	2·1
2	D, R or N on one occasion, missing PSE data on the remaining two occasions; *or* D, R, or N on one occasion and either D, R, N or A, B, X, NO on another occasion, with missing PSE data on the remaining one occasion, *or* D, R, or N on at least one occasion, and any combination of D, R, N, A, B, X, NO on one or two occasions	33	3·2
1	A or B on one occasion, A, B or X, NO on another occasion, with missing PSE data on the remaining one occasion: *or* A or B on at least one occasion, and any combination of A, B, X, NO on one or two occasions	2	0·2
		1037	100·0

S, Schizophrenic psychosis; P, Paranoid psychosis; O, Borderline and doubtful psychosis; M, Manic and mixed affective psychosis; D, Depressive psychosis; R, Retarded depression; N, Neurotic depression; A, Anxiety state; B, Obsessional neurosis; H, Hysterical conditions; X, Other; NO, No abnormality.

class on any two occasions and missing data on the other one, would be different, as regards course and outcome, from patients who had an S, P, or O class on one occasion only, and a non-psychotic CATEGO class on the remaining two occasions. The rest of the syndrome list presented in Table 4.13 was constructed in a similar way, and descriptive clinical labels were assigned to the different 'strings' before examining the course and outcome of the patients with those 'strings'. The clinical labels were chosen as a matter of convenience only, and have no terminological implications outside this context. The different combinations of CATEGO classes were grouped according to the following clinical concepts.

CATEGO 'string'	Corresponding clinical concept
10, 9	Schizophrenia
8.1, 8	Schizophrenia-like disorder
7, 6	Schizoaffective disorder
5, 4	Atypical affective disorder
3	Bipolar affective disorder
2	Unipolar affective disorder
1	Neurotic disorder

The numbers of patients and the percentages given in Table 4.13 indicate that with such use of the CATEGO classification (i.e. considering only the serial or consecutive PSE data and ignoring other diagnostically relevant information), not more than 5·5% of all included patients remain outside those sequences of CATEGO classes in which there is at least one S, P, or O. When the frequency with which each of the CATEGO 'strings' occurred in the course of the study in the individual catchment areas is examined it can be seen that 'string' 10 ('schizophrenia') was clearly predominant in all the centres in developed countries. In the centres in the developing countries 'string' 8 ('schizophrenia-

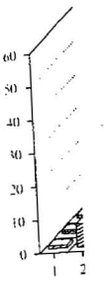

FIG. 4.3. 1

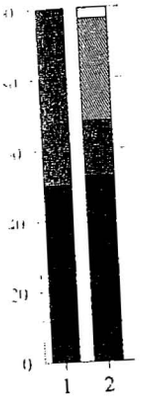

FIG. 4.4. Type
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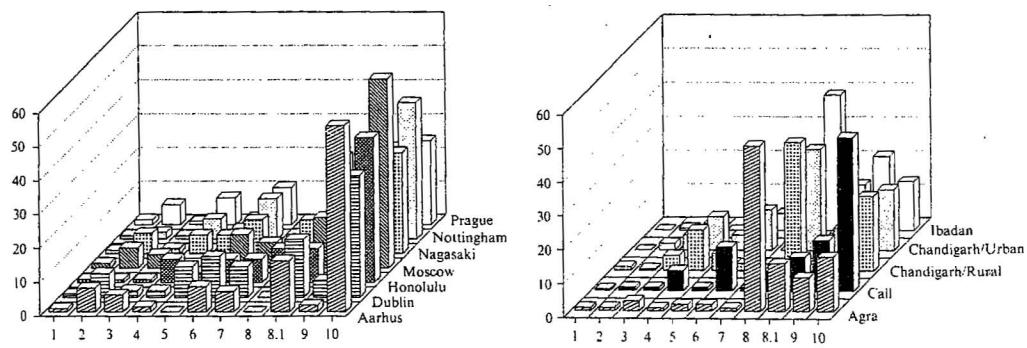

FIG. 4.3. Percentage distribution of specified sequences of CATEGO classes on initial and on two follow-up examinations by centre.

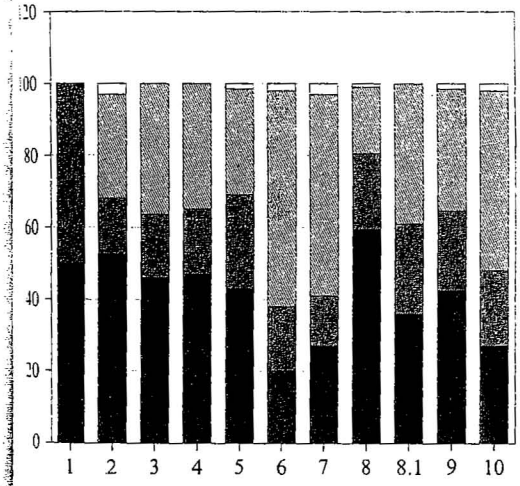

FIG. 4.4. Type of onset by sequence of CATEGO classes. ■, Acute; ▩, subacute; ▩, gradual; ▨, other or not rated.

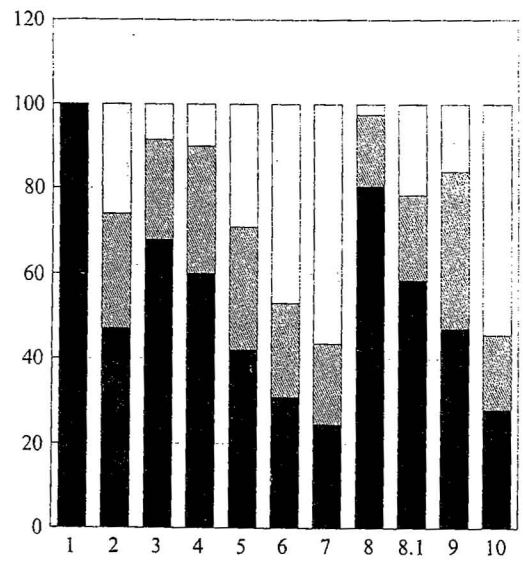

FIG. 4.5. Pattern of course by sequence of CATEGO classes. ■, Mild, patterns 1–3; ▩, intermediate, patterns 4, 5; ▨, poor, patterns 6, 7.

like psychosis') was modal in Agra, Chandigarh (rural and urban), and Ibadan, but not in Cali; in all of these centres, however, considerable percentages of the cases fell into categories 10 and 9. If anything, these data may indicate that the symptomatological manifestations of psychosis in the centres in developed countries tend to be more consistent over time than psychotic disorders in patients in the developing countries; further confirmation of this finding will however be necessary before it can be accepted with certainty.

The pooling of the data on patients in all of the centres shows that the CATEGO 'strings' are strongly associated with the mode of onset of the disorder (Fig. 4.4). For example, 50 or more per cent of the patients classified into types 8 ('schizophrenia-like'), 2 ('unipolar affective'), and 1 ('neurotic') had an acute onset, in contrast to types 10 ('schizophrenia'), and 7 and 6 ('schizoaffective'), in which over 50% of the patients had gradual onset.

No less important is the observed association between CATEGO 'strings' and the pattern of course. Fig. 4.5 indicates that 'mild' patterns of course (i.e. patterns 1, 2, and 3) characterize predominantly the disorders falling into the categories 1 ('neurotic'), 3 ('bipolar affective'), 4 ('atypical affective'), and 8 ('schizophrenia-like'), in contrast to the 'poor' patterns of course occurring most frequently in patients classified into categories 7 ('schizoaffective') and 10 ('schizophrenia').

Table 4.14. *Variables used in the analysis of predictors of course and outcome and number of patients for whom data were available*

Variables	Categories	Source of information	No. of patients
Outcome variables			
Pattern of course	Good – patterns 1–3	Synopsis table	500
	Intermediate – patterns 4–5		222
	Poor – patterns 6–7		334
Percentage follow-up time psychotic	< 15%	Synopsis table	527
	16-44%		266
	> 45%		276
Percentage follow-up time in complete remission	< 15%	Synopsis table	491
	16–44%		100
	> 45%		475
Percentage follow-up time in incomplete remission	< 15%	Synopsis table	571
	16–44%		168
	> 45%		325
Percentage follow-up time when social functioning was unimpaired	< 15%	Synopsis table	347
	16–44%		109
	> 45%		544
Percentage follow-up time in hospital	< 5%	Synopsis table	556
	6–15%		298
	> 15%		224
Percentage follow-up time on antipsychotic medication	< 15%	Synopsis table	265
	16–44%		196
	> 45%		617
Explanatory variables			
Gender	Male	PPHS	574
	Female		504
Age	< 25 years	PPHS	509
	> 25 years		569
Marital status	Single, widowed, divorced, married		655
	Common-law marriage, separated		408
Type of household	One person, unrelated persons	PPHS	116
	Nuclear family		694
	Extended family, joint family		231
Setting (level of industrialization)	Developing country	PPHS	604
	Developed country		474
Frequency of contact with relatives	None	PPHS	426
	Rare		328
	Frequent		273
Frequency of contact with close friends	None	PPHS	598
	Rare		251
	Frequent		171
Frequency of contact with casual friends	None	PPHS	458
	Rare		371
	Frequent		171
Avoidance of patient by family members	None	PPHS	705
	Some		138
	Marked		52
Avoidance of patient by relatives	None	PPHS	634
	Some		74
	Marked		26
	Increased contact		46
Avoidance of patient by close friends	None	PPHS	457
	Some		74
	Marked		36
	Increased contact		16
Avoidance of patient by casual friends	None	PPHS	556
	Some		91
	Marked		57
	Increased contact		14
Affective relationship to spouse (among married, common law, separated patients)	Never had close relationship (No interest shown)	PPHS	112
	Never close but showed interest		66
	Only casual contact		62
	Relationship before onset only		164
	Relationship after onset		43

Table 4.14. (*cont.*)

Variables	Categories	Source of information	No. of patients
Overall adjustment in childhood	Good adjustment	PPHS	690
	Transient problems		166
	Persistent problems		32
Overall adjustment in adolescence	Good adjustment	PPHS	593
	Transient problems		200
	Persistent problems		74
Street drug use	No use, none suspected	PPHS	878
	Sporadic use known or suspected		63
	Five or more instances known or suspected		82
Number of months since onset of disorder	Continuous variable	PPHS	986
CATEGO class	S+	PSE+CATEGO program	594
	Not S+		484
Main diagnosis			
Group 1	295.3	DPS	307
Group 2	295.1, 295.6		111
Group 3	296.7, 295.4, 295.2		328
Group 4	Other schizophrenia		159
Group 5	Non-schizophrenia (other diagnosis)		173
Type of onset	Acute	Synopsis table	405
	Sub-acute		216
	Slow		402

The conclusion which can be drawn from these data is that, while the CATEGO classification of PSE symptoms at the point of the initial examination does not predict the subsequent pattern of course, the sequential pattern of CATEGO classes determined on two or three follow-up examinations is predictively associated with an independently derived measure of the course of the disorder. Classes S, P, and O, if and when they recur, are clinical markers of a relatively poor prognosis, while the appearance of affective or neurotic CATEGO classes at any point in time, with or without an S, P, or O class on a single occasion, is associated with a more favourable evolution of the disorder.

It may be argued that in a general sense the CATEGO classes and the different patterns of course are not entirely unrelated (e.g. a CATEGO class representing psychosis could be *a priori* expected to be associated with a less favourable course than a class representing a neurotic illness). However, apart from the general criteria defining a psychotic and a non-psychotic episode, no specific symptomatology data were used in the operational definition of the pattern of course; the assessment of the latter was based only on a review of the longitudinal characteristics of the disorder. In contrast, the PSE/CATEGO assessment, as used in this study, presupposes the sampling of symptoms on a short-term (one month) basis, without any reference to the history of symptoms outside that period. The finding of an association between the pattern emerging from consecutive 'point' assessments by CATEGO, and the pattern emerging from longitudinal data should qualify the statement made above about the lack of predictive power for the CATEGO classification. It should also caution against the conclusion that symptomatology is not predictive of course and outcome; such a conclusion could only be made if a single cross-section of the mental state were considered. The data reported here advise strongly against prognostic judgements based on isolated cross-sections of the disorder.

PREDICTORS OF TWO-YEAR COURSE AND OUTCOME

The principal method used to identify predictors of two-year course and outcome was that of log-linear analysis. Log-linear modelling is a general term applying to a set of statistical techniques developed for analysing multidimensional cross-classifications. The particular technique used here is known as polytomous logit, or a log-odds model. It predicts the log-odds of a certain outcome measured by a discrete variable by using a linear combination of effects due to the explanatory variables.

The log-odds model makes no distributional

Table 4.15. *Effect of type of onset and setting on seven outcome variables*

Outcome variable	Explanatory variable	*N*	Effect on good outcome: Coefficient	Effect on good outcome: χ^2	Effect on good outcome: Estimated partial derivative	Effect on poor outcome: Coefficient	Effect on poor outcome: χ^2	Effect on poor outcome: Estimated partial derivative
Pattern of course	Type of onset							
	Acute	403	+0·445***	23·88	+0·111	−0·543***	24·92	−0·116
	Sub-acute	216	+0·052	0·25	+0·013	−0·197	2·74	−0·04
	Gradual[a]	389	−0·497		−0·124	+0·740		+0·158
	Setting							
	Developing country[a]	449	+0·227		+0·057	−0·290		−0·062
	Developed country	559	−0·227***	11·43	−0·057	+0·290***	14·63	+0·062
Percentage follow-up time in psychotic episode	Type of onset							
	Acute	404	+0·540***	34·27	+0·135	−0·573***	22·77	−0·107
	Sub-acute	215	+0·163	2·47	+0·041	−0·314*	5·50	−0·059
	Gradual[a]	398	−0·703·		−0·175	+0·887		+0·166
	Setting							
	Developing country[a]	450	−0·048		−0·010	+0·149		+0·028
	Developed country	567	+0·048	0·50	+0·010	−0·149	3·50	−0·028
Percentage follow-up time in complete remission	Type of onset							
	Acute	400	+0·495***	28·32	+0·123	−0·458***	21·96	−0·113
	Sub-acute	210	+0·240*	5·09	+0·059	−0·330**	8·71	−0·082
	Gradual[a]	405	−0·735		−0·182	+0·788		+0·195
	Setting							
	Developing country[a]	571	+0·355		+0·880	−0·524		−0·130
	Developed country	444	−0·355***	26·80	−0·088	+0·524***	54·28	+0·130
Percentage follow-up time in incomplete remission (and non-psychotic episode)	Type of onset							
	Acute	400	−0·020	0·05	−0·005	−0·047	0·21	−0·010
	Sub-acute	210	−0·068	0·42	−0·017	−0·009	0·01	−0·002
	Gradual[a]	404	+0·088		+0·022	+0·056		+0·012
	Setting							
	Developing country[a]	596	+0·306		+0·076	−0·542		−0·114
	Developed country	445	−0·306***	20·72	−0·076	+0·542***	48·23	+0·114
Percentage follow-up time in hospital	Type of onset							
	Acute	402	+0·162	2·29	+0·040	−0·054	0·18	+0·008
	Sub-acute	213	−0·019	0·02	−0·005	−0·128	0·81	+0·021
	Gradual[a]	411	−0·143		−0·036	+0·182		−0·030
	Setting							
	Developing country[a]	574	+1·243		+0·310	−1·423		−0·235
	Developed country	452	−1·243***	245·49	−0·310	+1·423***	91·30	+0·235
Percentage follow-up time on medication	Type of onset							
	Acute	402	+0·313**	8·76	+0·057	−0·203*	4·43	−0·049
	Sub-acute	213	−0·108	0·70	−0·020	+0·109	0·94	+0·027
	Gradual[a]	411	−0·205		−0·037	+0·094		+0·023
	Setting							

Percentage follow-up time on antipsychotic medication								
Type of onset								
Acute	402	+0·313**	8·76	+0·057	−0·203*	4·43	−0·049
Sub-acute	213	−0·108	0·70	−0·020	+0·109	0·94	+0·027
Gradual[a]	411	−0·205		−0·037	+0·094		+0·023
Setting							
Developing country[a]	574	+0·685		+0·125	−0·792		−0·193
Developed country	452	−0·685***	70·39	−0·125	+0·792***	125·72	+0·193
Percentage follow-up time in unimpaired social functioning							
Type of onset							
Acute	375	+0·447***	21·10	+0·111	−0·478***	19·30	−0·107
Sub-acute	198	+0·202	3·35	+0·050	−0·170	1·98	−0·038
Gradual[a]	380	−0·649		−0·161	+0·648		+0·145
Setting							
Developing country[a]	446	+0·204		+0·051	−0·433		−0·097
Developed country	507	−0·204**	8·40	−0·051	+0·433***	32·23	+0·097

[a] Excluded category; * significant at 0·05 level; ** significant at 0·01 level; *** significant at 0·001 level.

assumptions and can handle interactions between variables easily. It differs from the more conventional methods of analysing the relationships between categorical variables, such as the chi-square tests, in the manner in which the dependent variable is represented in the model. While the traditional methods represent the dependent variables in terms of proportions of subjects falling into specified categories, the log-odds model uses the natural logarithm of the ratio of frequencies for any two categories of the dependent (outcome) variable. The log-odds model, therefore, explores how the odds (expressed in a log form) that a subject will appear in one outcome category rather than in another are linked to the explanatory, or predictor, variables. By comparing the natural logarithms of the odds, rather than the proportions of cases in each category, the log-odds model has the effect that the distance between the proportions is 'stretched' as they approach the values of zero and one. For example, in a log-odds model a distance between 0·1 and 0·2 will be about twice the distance between 0·5 and 0·6 (Kritzer, 1979).

The log-odds model for polytomous data, when the dependent variable has n categories, can be written as a set of $n-1$ equations:

$$\ln \frac{P_j}{1-P_j} = u_j + \sum_i \beta_{ij} X_i;$$

where j represents categories of the dependent variable, P_j is the frequency of responses in category j, u_j is a consonant, X_is are the explanatory variables, and β_{ij}s are the coefficients to be estimated. The model was implemented using maximum likelihood techniques and the SAS version 5 CATMOD procedure.

The results presented below include both the estimated coefficients β_{ij} as well as the estimated partial derivative evaluated at the sample mean which can be used to approximate the percentage point change in the dependent variable per unit change in the explanatory variable. (For categorical variables the formula for the estimated partial derivative is an approximation – Peterson & Kronmal, 1985.)

Table 4.14 lists all variables used in the predictor analysis and their categorization. Seven measures of course and outcome were used, namely pattern of course, percentage of the follow-up period during which the subject

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