CHAPTER 1

Diagnosis and revision of the classification systems

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Information Box

- Like most of psychiatry's diagnostic concepts represented in ICD-10 and DSM-IV, the 'disease' schizophrenia is a working hypothesis that may not meet the criteria of unitary aetiology or pathogenesis, and its diagnostic criteria should be regarded as provisional.
- There is a growing understanding that the complex syndromal spectrum of schizophrenia comprises end-point phenotypes for heterogeneous gene networks, pathophysiological pathways and environmental modifiers.
- There is little evidence that schizophrenia is a discrete category, separated from other disorders by 'natural' boundaries, yet proposals to replace the category with a dimensional construct are premature.
- Although schizophrenia cannot yet be described as a valid disease category, the diagnostic concept of schizophrenia and its spectrum provides information of great utility to clinicians and continues to generate testable research hypotheses.

INTRODUCTION

There is a broad consensus that schizophrenia is a complex mental disorder with variable phenotypic expression and poorly understood multifactorial aetiology, involving a significant but likely heterogeneous genetic contribution; environmental factors interacting with the genetic susceptibility; and – in many cases – early

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neurodevelopmental aberrations that precede the onset of overt psychotic symptoms. Schizophrenia occurs in diverse populations at comparable rates [1,2], with a lifetime prevalence of ∼0.4% [3] and, as far as archival data are available, without significant secular changes in its incidence [4]. This is consistent with an ancient origin of the disorder. At present, schizophrenia accounts for at least 2.3% of the global burden of disease and disability, yet, globally, a large proportion of the people affected by the disorder still remain untreated [5].

Diagnostic concepts play a critical role in the management and treatment of schizophrenia patients: in research aiming to identify risk factors and causal mechanisms; and in attempts at resolving contentious issues, such as the nature of comorbidity and the relationships between schizophrenia and other, partly overlapping disorders. A major difficulty hampering progress in this work is the inherent weakness of the diagnostic concept of schizophrenia, in that it remains predicated on the assumption of an underlying but still unknown disease process. Most of the criteria defining schizophrenia are symptom-based, relying on the clinician's interpretation of patients' subjective experiences. As yet, there is no objective diagnostic test or a validated biological marker that could unequivocally support clinical decision-making or biological and epidemiological research. Notwithstanding the current availability of explicit diagnostic criteria, incorporated in the World Health Organisation classification of mental disorders, ICD-10 [6] and the Diagnostic and Statistical Manual of the American Psychiatric Association, DSM-IV [7], disagreements persist regarding the delimitation of schizophrenia from other psychoses, and from affective and neurodevelopmental disorders. Similarly, there is no consensus on the classification of its subclinical forms, such as schizotypal disorder, or its pre-clinical manifestations, such as the putative schizophrenia risk syndrome. Other contentious issues concern the utility of a categorical classification of the disorder as compared to descriptive symptom dimensions or subtypes based on quantitative cognitive traits. The present chapter provides an overview of the origin, evolution, and current state of the concept of schizophrenia, and aims to foreshadow some of the options worth considering in the process of revision of the major diagnostic classifications.

ORIGIN AND EVOLUTION OF THE CONCEPT OF SCHIZOPHRENIA

The disease concept of schizophrenia is relatively recent, as compared with mental afflictions known since antiquity, such as melancholia, mania, or 'insanity'. Only by mid-nineteenth century did European psychiatrists begin singling out from the bulk of 'insanity' a particular disorder of unknown causation, typically affecting young people, and often progressing to chronic deterioration. In France, Morel [8] referred to such cases as '*démence précoce*', while in Scotland, Clouston [9] coined the term 'adolescent insanity'. In Germany, Kahlbaum [10] delineated the catatonic syndrome, and his disciple Hecker [11] described hebephrenia. However, it was

Emil Kraepelin (1856–1926) who integrated those quite varied clinical pictures into a single nosological entity under the name of *dementia praecox* [12] on the basis of his systematic observations of a large number of clinical cases presenting with variable cross-sectional features but commonly tending towards a course that ultimately resulted in cognitive and behavioural decline.

Kraepelin's 'clinical forms'

Kraepelin acknowledged the diversity of the clinical pictures subsumed under *dementia praecox* and articulated nine different 'clinical forms' (Table 1.1). He emphasised that 'we meet everywhere the *same fundamental disorders* in the

Table 1.1 Emil Kraepelin's 'clinical forms'

- **Dementia praecox simplex**
  (*'Impoverishment and devastation of the whole psychic life which is accomplished quite imperceptibly'*)
- **Hebephrenia**
  (Insidious change of personality with shallow capricious affect, senseless and incoherent behaviour, poverty of thought, occasional hallucinations and fragmentary delusions, progressing to profound dementia)
- **Depressive dementia praecox (simple and delusional form)**
  (Initial state of depression followed by slowly progressive cognitive decline and avolition, with or without hypochondriacal or persecutory delusions)
- **Circular dementia praecox**
  (Prodromal depression followed by gradual onset of auditory hallucinations, delusions, marked fluctuations of mood and aimless impulsivity)
- **Agitated dementia praecox**
  (Acute onset, perplexity or exaltation, multimodal hallucinations, fantastic delusions)
- **Periodic dementia praecox**
  (Recurrent acute, brief episodes of confused excitement with remissions)
- **Catatonia**
  ('Conjunction of peculiar excitement with catatonic stupor dominates the clinical picture' in this form, but catatonic phenomena frequently occur in otherwise wholly different presentations of dementia praecox)
- **Paranoid dementia (mild and severe form)**
  (The essential symptoms are delusions and hallucinations. The severe form results in a 'peculiar disintegration of psychic life', involving especially emotional and volitional disorders. The mild form is a very slowly evolving 'paranoid or hallucinatory weak-mindedness' which 'makes it possible for the patient for a long time still to live as an apparently healthy individual')
- **Schizophasia (confusional speech dementia praecox)**
  (Cases meeting the general description of dementia praecox but resulting in an end state of 'an unusually striking disorder of expression in speech, with relatively little impairment of the remaining psychic activities')

different forms of *dementia praecox* . . . in very varied conjunctions, even though the clinical picture may appear at first sight ever so divergent'. [13]. The 'fundamental disorders' included cognitive deficit (a 'general decay of mental efficiency') and executive dysfunction ('loss of mastery over volitional action'). Kraepelin never issued a definitive list of diagnostic criteria for *dementia praecox* and was rather sceptical about the existence of 'pathognomonic' symptoms. He believed that the validation of the provisional disease entity, which he always regarded as provisional, would ultimately come from neuropathology, physiology, and biological chemistry of the brain. Towards the end of his career, he even considered abandoning the categorical disease formulation of schizophrenia and manic-depressive illness as distinct disorders and replacing the dichotomy with an essentially dimensional model in which schizophrenic and affective syndromes 'do not represent the expression of particular pathological processes, but rather indicate the areas of our personality in which these processes unfold' [14]. In the same paper Kraepelin proposed three hierarchically arranged 'registers' or strata of psychopathology – affective, schizophrenic and encephalopathic – which would recombine in many different ways to produce the manifold syndromes of the major mental disorders. Later, this concept became known in German psychiatry as the *'Schichtenregel'* (the *strata* rule).

Bleuler's 'group of schizophrenias'

Eugen Bleuler (1857–1939) modified Kraepelin's original concept by adding to the scope of *dementia praecox* clinical illnesses that did not evolve into a 'terminal state' of deterioration, which Kraepelin considered to be the hallmark of the disease. Having coined the term schizophrenia to replace *dementia praecox*, Bleuler [15] stated that schizophrenia 'is not a disease in the strict sense, but appears to be a group of diseases . . . Therefore we should speak of schizophrenias in the plural'. Bleuler introduced a fundamental distinction between *basic* (obligatory) and *accessory* (supplementary) symptoms of the disorder. While the accessory symptoms comprised the delusions and hallucinations which today are given preeminent diagnostic prominence in both ICD-10 and DSM-IV as 'positive' symptoms, Bleuler's basic symptoms included thought and speech derailment ('loosening of associations'), volitional indeterminacy ('ambivalence'), affective incongruence, and withdrawal from reality ('autism'). It was the basic symptoms that, according to Bleuler, gave schizophrenia its distinctive diagnostic profile. Along with the 'latent' schizophrenias, which represented attenuated forms of the basic symptoms and were mainly manifested as aberrant personality traits, he also added to the 'broader concept' of schizophrenia atypical depressive or manic states, Wernicke's motility psychoses, reactive psychoses, and other non-organic, non-affective psychotic disorders, on grounds that 'this is important for the studies of heredity', thus foreshadowing the notion of schizophrenia spectrum disorders.

Leonhard's 'endogenous psychoses'

In a clinical tradition originating with Wernicke and Kleist, who had proposed grouping psychotic illnesses on the basis of a presumed localised cerebral dysfunction, Karl Leonhard (1904–88) [16] developed an elaborate classification of the 'endogenous' psychoses which departed substantially from the Kraepelinian and Bleulerian nosology. Leonhard defined sharply delineated disease entities, based on a detailed psychopathology that emphasised objective signs, such as psychomotor behaviour, course and outcome, as well as family history. The nonaffective psychoses were split into 'systematic' and 'unsystematic' forms of schizophrenia, and a third group of 'cycloid' psychoses, each containing further subtypes (Table 1.2). While the 'unsystematic' schizophrenias were considered to be primarily genetic, hereditary factors played a secondary role in the cycloid psychoses and in the 'systematic' schizophrenias, which were presumed to be exogenously determined, for example, by maternal obstetric complications or early failure of social learning. Leonhard's classification neither expanded, nor constricted the boundaries of schizophrenia, but carved the schizophrenia spectrum in a different way.

Classification of psychoses in French psychiatry

At the time when Kraepelin's ideas were gaining wide, though not uncontested, acceptance in Europe and North America, French psychiatrists [17] maintained a distance from the prevailing *dementia praecox* trend. Following the French tradition of a refined nosography, the non-affective psychotic disorders were divided into three major classes: (i) '*bouffée délirante polymorphe aiguë*' (acute polymorphic delusional psychosis); (ii) '*psychose hallucinatoire chronique*' (chronic hallucinatory psychosis); and (iii) '*schizophrenie chronique*' (chronic schizophrenia). The latter category, though influenced by Bleuler, was only reserved for the late, presumably irreversible, stages of the chronic hallucinatory psychosis. French psychiatrists placed much emphasis on the age at onset and the mode of onset (acute versus insidious). In ICD-10 (but not in DSM-IV), the French concept of acute polymorphic delusional psychosis was considered to be closely similar to Leonhard's cycloid psychoses and was incorporated as an inclusion term in the classification.

Other post-Kraepelinian and post-Bleulerian subtypes and dichotomies

During the next several decades, there was a growing realisation that schizophrenia was indeed a broad grouping of clinically heterogeneous disorders. A number of

Table 1.2 Karl Leonhard's classification of the non-affective endogenous psychoses

I. Group of systematic schizophrenias
(Insidious onset, auditory and somatic hallucinations, delusions, early blunting of affect, continuous unremitting course, personality deterioration)

Paraphrenias
(Auditory hallucinosis, audible thoughts, thought broadcast, passivity experiences, delusional misidentifications, falsifications of memory)
Hebephrenias
(Extreme autistic withdrawal, flat affect, impoverished or disorganised speech and behaviour)
Catatonias
(Excessive parakinesias, mannerisms, verbigeration, posturing, stereotypies, mutism, auditory hallucinations)

II. Group of unsystematic (atypical) schizophrenias
(Rapid onset, relatively preserved affect, remitting course, mild personality deterioration)

Affect-laden paraphrenia
(Paranoid delusions with affective loading)
Cataphasia (schizophasia)
(Incoherent, pressured speech but well-organised behaviour)
Periodic catatonia
(Episodic hyper- or hypokinesia, mixed excitatory and hallucinatory symptoms)

III. Group of cycloid psychoses
(Sudden onset, pervasive delusional mood, multimodal hallucinations, labile affect, polarity of manifestations, typically complete recovery from episode)

Anxiety-happiness psychosis
(Extreme shifts of affect, polarity intense fear – ecstatic elation)
Motility psychosis
(Impulsive hypermotility – psychomotor inhibition)
Confusion psychosis
(Incoherent pressure of speech – mutism)

sub-nosological distinctions were proposed, based on a mix of criteria that included symptomatology, course, or presumed aetiology (Table 1.3). [18,19,20,21,22,23]

In what could be regarded as prototype diagnostic criteria, Kurt Schneider [24] proposed that nine groups of psychotic manifestations, designated as 'first-rank symptoms' (FRS), had a 'decisive weight' in the diagnosis of schizophrenia: audible thoughts; voices arguing about, or discussing the patient; voices commenting on the patient's actions; experiences of influences on the body; thought withdrawal

Table 1.3 Post-Kraepelinian and post-Bleulerian subtypes and dichotomies

Schizophrenia subtypes	Descriptive features	Authors
Schizoaffective disorder	Acute onset of hallucinations and delusions accompanied by distinct and prominent manic or depressive symptoms	Kasanin [18]
Schizophreniform psychoses	Cases initially diagnosed as schizophrenia but lacking features such as affective flattening, autistic withdrawal, disturbances of volition and chronic course	Langfeld [19]
Process / non-process schizophrenia	Process: introverted premorbid personality, insidious onset, affective blunting, primary delusions (often bizarre), somatic delusions. Non-process: extroverted premorbid personality, absence of gradual personality changes, acute onset with marked excitement, elation, anxiety or depression, good prognosis	Stephens & Astrup [20]
Paranoid-nonparanoid schizophrenia	Paranoid: later age of onset, well-organised delusions or hallucinations, absence of affective changes. Non-paranoid: earlier age of onset, flat or inappropriate affect, formal thought disorder, poorer prognosis	Tsuang & Winokur [21]
Positive-negative schizophrenia ("Type I" and "Type II"	Type I: positive symptoms (hallucinations, delusions, formal thought disorder). Type II: negative symptoms (social withdrawal, loss of volition, affective flattening, poverty of speech)	Crow [22]
Deficit-nondeficit schizophrenia	Deficit subtype: enduring primary negative symptoms that cannot be explained as sequelae of depression or other psychopathology	Carpenter *et al.* [23]

and other interference with thought; thought broadcast (diffusion of thought); delusional perception; and other experiences involving 'made' impulses and feelings experienced as caused by an outside agency. Due to the specificity with which they were described, the FRS were later adopted and incorporated in the Research Diagnostic Criteria, RDC [25]; DSM III [26]; and ICD-10 [6].

The schizophrenia spectrum concept

The observation that several different disorders tend to cluster among biological relatives of individuals with clinical schizophrenia has been supported by epidemiological and family studies suggesting that the genetic liability to schizophrenia is shared with liability to other related syndromes [26,27]. The most prominent among these syndromes is schizotypal disorder. The term 'schizotypy', introduced by Rado [27] and Meehl [28], refers to a personality characterised by anhedonia, ambivalence, 'interpersonal aversiveness', body image distortion, 'cognitive slippage', and sensory, kinaesthetic or vestibular aberrations. Chapman *et al.* [29] designed scales to measure perceptual aberrations and 'magical ideation' as traits predicting 'psychosis proneness'. These constructs were later incorporated into the DSM-III category of schizotypal personality disorder (SPD). The frequent occurrence of SPD among first-degree relatives of individuals with schizophrenia has been replicated in the Roscommon epidemiological study [30], which added to the schizophrenia spectrum further disorders co-segregating within families. The resulting 'continuum of liability' includes: (i) 'typical' schizophrenia; (ii) schizotypal and paranoid personality disorders; (iii) schizoaffective disorder, depressed type; (iv) other non-affective psychotic disorders (schizophreniform, atypical psychosis); and (v) psychotic affective disorders. Evidence from family and twin data suggests that the manifestations of SPD fall into two genetically separate clusters: a 'negative' cluster (odd speech and behaviour, inappropriate affect and social withdrawal), more common among relatives of schizophrenic probands, and a 'positive' cluster (magical ideation, brief quasi-psychotic episodes), associated with increased incidence of affective disorders in relatives. 'Negative' schizotypy may indeed represent a subclinical *forme fruste* of schizophrenia with attenuated cognitive deficits and mild brain structural abnormalities.

Statistically derived clusters and symptom dimensions

Factor analysis and related statistical methods have been used to extract covariances from a small number of latent factors which could account for the interrelationships of symptoms and explain a proportion of their variance. A three-factor solution has been proposed [31] and subsequently replicated [32–34], based on a relatively small number of input variables (SANS/SAPS scores). In this model, negative symptoms load on a single factor of 'psychomotor poverty', while positive symptoms split into a delusions-and-hallucinations factor ('reality distortion') and a thought-and-speech disorder factor ('disorganisation'). In a large sample of schizophrenia probands, McGrath *et al.* [35] identified five factors (positive, negative, disorganised, affective and early onset/developmental). In another series of factor analyses based on an expanded list of 64 psychopathological symptoms, Cuesta and Peralta

[36] concluded that a hierarchical 10-dimensional model provided the best fit on statistical and clinical grounds. However, the output of factor analyses of symptomatology depends on the content of the input, for example, studies using SANS and SAPS produce different solutions from those based on scales such as PANSS, BPRS or OPCRIT. Factor solutions, therefore, are not unique and the number of factorial dimensions that describe parsimoniously the clinical presentation varies, depending on the particular selection of symptoms and measurement methods. Therefore, factor-analytical studies suggesting 'established' dimensions or syndromes of schizophrenia should be viewed with caution, considering the diversity of clinical populations and the limitations of the instruments used to generate the input data. Similar considerations apply to the methods of cluster analysis which group individuals on the basis of maximum shared characteristics.

Latent class analysis (LCA) assumes the existence of a finite number of mutually exclusive and jointly exhaustive groups of individuals. A latent class typology of schizophrenia, proposed by Sham *et al.* [37], using data on 447 patients with nonaffective psychoses, ended up with three subgroups: a 'neurodevelopmental' subtype resembling the hebephrenic form of the disorder (poor premorbid adjustment, early onset, prominent negative and disorganised features); a 'paranoid' subtype (less severe, better outcome); and a 'schizoaffective' subtype (dysphoric symptoms). In an epidemiological sample of 343 cases of schizophrenia and affective disorders, Kendler *et al.* [38] identified six latent classes, broadly corresponding to the clinical forms of 'Kraepelinian' schizophrenia: major depression, schizophreniform disorder; schizoaffective disorder (manic), schizoaffective disorder (depressed) and hebephrenia. Similar results, using a combination of principal component analysis and LCA in a sample of 387 patients with psychoses have been reported by Murray *et al.* [39].

In contrast to conventional LCA, a form of latent structure analysis, known as grade of membership (GoM), allows individuals to be members of more than one disease class and represents the latent groups as 'fuzzy sets' [40,41]. The GoM model simultaneously extracts from the data matrix a number of latent 'pure types' and assigns to each individual a set of numerical weights quantifying the degree to which that individual resembles each one of the identified pure types. When applied to the symptom profiles of 1065 cases in the WHO International Pilot Study of Schizophrenia [42], the method identified eight pure types of which five were related to schizophrenia, two to affective disorders and one to patients in remission, all showing significant associations with course and outcome variables used as external validators.

SCHIZOPHRENIA IN ICD-10 AND DSM-IV

While both DSM-IV and ICD-10 are widely regarded as authoritative documents providing evidence-based definitions and diagnoses of mental disorders, they have

evolved in different contexts and address partially overlapping but different constituencies [43].

Origins of the two classifications

The International Classification of Diseases (ICD), of which Chapter 5, Mental and Behavioural Disorders is a part, is a statutory responsibility of the World Health Organisation (WHO) as an intergovernmental agency that aims to provide a common language for the reporting of all known diseases and health states across the world's populations. The DSM is essentially a national diagnostic classification of mental disorders, developed by a non-governmental professional body, the American Psychiatric Association (APA), and widely adopted by US government agencies, such as the Food and Drugs Administration and the Social Security Administration, as well as by the health insurance industry and the American legal system. A major difference between the two classifications is that, in contrast to DSM-IV, which provides a single set of 'operational' diagnostic criteria for all potential users, ICD-10 was designed as a 'family' of inter-related versions, addressing different users. While the ICD-10 Clinical Descriptions and Diagnostic Guidelines (ICD-10 CDDG) is the conceptual core of the system, the more restrictive Diagnostic Criteria for Research (ICD-10 DCR) are designed for use in a more narrowly constrained context.

Both DSM-IV and ICD-10 are descendants of the Kraepelinian nosology

The basic concept underlying Kraepelin's classification of psychoses was the disease entity, postulating close relationships between clinical symptoms, the longitudinal course and outcome, and brain pathology. Notwithstanding decades of clinical, neuroscience and genetic research, the validating criteria of the nosological entity of schizophrenia remain to this day essentially restricted to the internal cohesion of the clinical picture and the regularities of course and outcome. There are both similarities and differences in the way the two classifications define schizophrenia (Tables 1.4 and 1.5). While ICD-10 explicitly acknowledges schizophrenia as a group of disorders, the DSM-IV criteria implicitly suggest a unitary view of the disorder. However, both sets of criteria refer to: (i) characteristic symptoms present in the cross-section of the clinical picture, weighted differentially for diagnostic significance ('at least one. . .' or 'two or more. . .'); (ii) the duration of symptoms required for a reliable ascertainment; and (iii) the longitudinal pattern of course. While both systems require persistence of 'active phase' diagnostic symptoms for at least one month, ICD-10 lays greater emphasis on the presence of Schneiderian first-rank symptoms. An important difference is the DSM-IV requirement of at

Table 1.4 ICD-10 / F2 group of disorders

Schizophrenia (F20): Diagnostic Criteria for Research
At least one. . .
(a) thought echo, insertion, withdrawal or broadcasting
(b) delusion of control, influence or passivity
(c) hallucinatory voices – running commentary or discussing the patient
(d) persistent delusions – culturally inappropriate and completely impossible

Or at least two. . .
(a) persistent hallucinations in any modality, when accompanied by delusions
(b) neologisms, breaks or interpolations in the train of thought, incoherence
(c) catatonic behaviour
(d) 'negative' symptoms: apathy, paucity of speech, emotional blunting or incongruity

. . .**should be present for most of the time during an episode of psychotic illness lasting for at least one month**

Pattern of course (period of observation at least one year)
Continuous (no remission of psychotic symptoms)
Episodic with progressive deficit ('negative' symptoms in the intervals)
Episodic with stable deficit (persistent but non-progressive 'negative' symptoms)
Episodic remittent (complete remissions between psychotic episodes)
Incomplete remission
Complete remission
Other
Course uncertain, period of observation too short

Clinical subtypes
Paranoid
Hebephrenic
Catatonic
Undifferentiated
Post-schizophrenic depression
Residual
Simple
Other
Unspecified

Other F2 disorders
Schizotypal disorder (F21)
Persistent delusional disorders (F22)
Acute and transient psychotic disorders (F23)
Induced delusional disorder (F24)
Schizoaffective disorders (F25)
Other nonorganic psychotic disorders (F28)
Unspecified nonorganic psychosis (F29)

Table 1.5 DSM-IV-TR Schizophrenia and other psychotic disorders

A. Two (or more) *characteristic symptoms*, each present for a significant portion of time during a one-month period (or less if successfully treated):
(1) delusions; (2) hallucinations; (3) disorganised speech (derailment or incoherence); (4) grossly disorganised or catatonic behaviour; (5) negative symptoms (affective flattening, alogia, or avolition). (*Only one symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary. . .or two or more voices conversing with each other).*
B. Social/occupational dysfunction
C. Duration: Continuous signs of the disturbance persist for at least six months, including at least one month of active-phase symptoms and may include periods of prodromal or residual symptoms. During prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more *Criterion A* symptoms in an attenuated form (for example, odd beliefs, unusual perceptual experiences).
D. Schizoaffective and mood disorder exclusion
E. Substance/general medical condition exclusion
F. Relationship to a pervasive developmental disorder: If there is a history of Austistic Disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month.

Subtypes:
Paranoid (295.30)
Disorganised (295.10)
Catatonic (295.20)
Undifferentiated (295.90)
Residual (295.60)

Longitudinal course:
Episodic with interepisode residual symptoms (prominent negative symptoms may be added)
Episodic with no interepisode residual symptoms
Continuous (prominent negative symptoms may be added)
Single episode in partial remission (prominent negative symptoms may be added)
Single episode in full remission
Other unspecified pattern

Other disorders within the same group:
Schizophreniform disorder (with / without good prognostic features) (295.40)
Schizoaffective disorder (bipolar or depressive type) (295.70)
Delusional disorder (297.1)
Brief psychotic disorder (with / without stressor, or with postpartum onset) (298.8)
Shared psychotic disorder (297.3)
Psychotic disorder due to a general medical condition (293.xx)
Substance-induced psychotic disorder (291xx or 292.xx)
Psychotic disorder not otherwise specified (298.9)

least six months duration of *any* disturbances (including prodromal and residual symptoms) for a confident diagnosis, relegating cases of shorter duration to a diagnosis of schizophreniform disorder that could be revised at a later stage. A period of four weeks is considered in ICD-10 to be sufficient to eliminate the majority of acute, non-schizophrenic psychotic episodes associated with substance use. Another difference between the two classifications is related to the DSM-IV Criterion B which requires the presence of significant social or occupational dysfunction as part of the definition of schizophrenia. In contrast, the explicit principle applying to all ICD-10 diagnoses is that social and occupational functioning is context-dependent and not an invariant attribute of the clinical syndrome. On the whole, it is assumed, though not empirically demonstrated, that the DSM-IV criteria of six months duration and social/occupational dysfunction tend to select cases of more severe or chronic illness than the ICD-10 criteria.

Importantly, DSM-IV and ICD-10 are not systematic classifications in the usual sense in which that term is applied in biology. Essentially, they are augmented *nomenclatures*, that is, lists of names for conditions and behaviours, supplied with explicit rules about how these names should be assigned and used. As such, they are useful tools of communication and can play a pragmatically useful role in psychiatric research, clinical management and teaching.

CRITERIA FOR ASSESSING THE DIAGNOSTIC CLASSIFICATION OF SCHIZOPHRENIA

Positive impact and unintended adverse effects

Four decades after the introduction of explicit diagnostic criteria and rule-based classifications such as DSM-III [26], ICD-10 [6] and DSM-IV [7], it is now possible to examine the impact of these tools on psychiatric practice and research. The worldwide adoption of these classification systems has influenced several domains of professional practice: (i) a standard frame of reference is now available to clinicians, enabling them to achieve better diagnostic agreement; (ii) more rigorous diagnostic standards have become the norm in psychiatric research; (iii) the teaching of psychiatry to medical students, trainee psychiatrists and other mental health workers is based on an international reference system which provides a 'common language'; (iv) open access to the criteria used by mental health professionals has improved communication with the users of services, carers, and the public at large. These achievements, however, have not been without a downside.

First, once a diagnostic concept like schizophrenia has been 'operationalised' for general use, it tends to become reified. Professionals and members of the general public too easily assume that it is an entity which explains the patient's symptoms and whose validity need not be questioned. The mere fact that a diagnostic concept

is listed in an influential official nomenclature and provided with an operational definition tends to encourage this insidious reification.

Secondly, for most of the diagnostic rubrics of DSM-IV and ICD-10 (which clearly do not qualify as diseases), both classifications avoid discussing precisely what is being classified. DSM-IV explicitly rejects the 'misconception that a classification of mental disorders classifies people' and states that 'actually what are being classified are *disorders* that people have' [7]. The term 'disorder', first introduced in DSM-I in 1952, circumvents the problem that the information from which most of the diagnostic rubrics are constructed consists primarily of reported subjective experiences and patterns of behaviour. Some of those rubrics correspond to syndromes in the medical sense, but many appear to be isolated symptoms, habitual behaviours, or personality traits.

Thirdly, the fragmentation of psychopathology into a very large number of 'disorders' – of which many are merely symptoms – leads to a proliferation of comorbid diagnoses which clinicians are forced to use in order to describe their patients. This blurs the distinction between true comorbidity (co-occurrence of aetiologically independent disorders) and spurious comorbidity. masking complex but essentially unitary *syndromes*. It is not surprising, therefore, that recent epidemiological and clinical research leads to the conclusion that disorders, as defined in the current versions of DSM and ICD, have a strong tendency to co-occur, which suggests that 'fundamental assumptions of the dominant diagnostic schemata may be incorrect' [44].

Fourthly, while eminently useful for specific purposes of communication, the DSM-IV and ICD-10 criteria are no substitute for clinical acumen. The belief that 'operationalised' criteria have once and for all resolved the problem of reliability of psychiatric diagnosis may be illusory, if the validity of the assessment of symptoms and signs in actual clinical practice can be shown to be questionable. An unfortunate adverse effect of both classifications is the alienation of the practice of clinical psychiatry from its roots in psychopathology and phenomenology. To quote a perceptive commentator [45], 'since the publication of DSM-III in 1980, there has been a steady decline in the teaching of careful clinical evaluation that is targeted to the individual person's problems and social context and that is enriched by a good general knowledge of psychopathology. . . by 2005, the decline has become so severe that it could be referred to as 'the death of phenomenology in the United States.'

Clinical relevance and cognitive ease of use

The clinical relevance of a diagnostic concept refers to its scope (coverage), capacity to describe attributes of individuals (such as clinical severity of the disorder, impairments and disabilities), and its ease of application in the various settings in which people with mental health problems present for assessment or treatment.

In the instance of schizophrenia, the diagnostic system should be capable of not only identifying the broad syndrome but also differentiating between degrees and variants of its expression in individual patients and the severity of the associated impairments and disabilities. This implies that the DSM / ICD multiaxial models of diagnostic formulation should not be abandoned but rather further refined. By and large, a multiaxial arrangement allowing separate and independent assessment of psychopathological syndromes, personality characteristics, somatic morbidity, psychosocial precipitants or complicating factors, cognitive functioning and overall impairment or disability, should be capable of 'individualising' the diagnostic assessment. However, the content of information to be recorded on individual axes will require substantial refinement. For example, the axes that are particularly problematic in the present ICD and DSM multiaxial systems are those concerned with the level of cognitive functioning and personality.

As classifications are basically devices for reducing cognitive load, a diagnostic classification in psychiatry should also be examined from the point of view of its capacity to integrate diverse observations with a minimum number of assumptions, concepts and terms [46] and ease of evocation of its categories in clinical situations. The system should also allow the clinician to use the type of knowledge usually described as clinical experience or judgement, and enable appropriate decisions to be made under conditions of uncertainty, incomplete data, and time pressure.

Utility in research

Both DSM-III and its successors and, to a lesser extent, ICD-10, were quickly adopted by researchers as rigorous diagnostic standards. However, the performance of a classification as a research tool needs to be evaluated against a number of different requirements that are not always compatible – for example, the type of diagnostic criteria needed for clinical trials or for biological research may not be suitable for epidemiological surveys.

The use of restrictive DSM-IV or ICD-10 definitions, rather than of broader clinical concepts, as sampling criteria in recruiting subjects for clinical or epidemiological research, carries the risk of systematic error due to a selective exclusion of segments of the syndrome. For example, the DSM-IV requirement of at least six months duration of symptoms plus the presence of social or occupational dysfunction for a diagnosis of schizophrenia is likely to bias the selection of populations for biological, therapeutic, or epidemiological longitudinal studies. It would certainly make little sense to study the variation in course and outcome in a clinical population that had already been pre-selected for chronicity by applying the six-month duration criterion. Studies of the molecular genetics of psychoses, usually involving collaborative consortia of investigators and a considerable investment of resources, are predicated on the validity of DSM-IV criteria. However, so far no susceptibility genes have been definitively identified and few of the many reported linkage or

association findings have been replicated [47]. In the absence of genes of major effect, the chances of detecting multiple genes of small or moderate effect depend critically on the availability of phenotypes mapping onto characteristic brain dysfunction or morphology. The 'disorders' of current symptom-based classifications may be masking substantial phenotypic variation in symptomatology and outcome which would hinder genetic analysis. In addition to a better syndromal definition at the clinical symptom and course level, future developments of diagnostic systems for research are likely to involve supplementing the clinical diagnosis with measures of brain morphology and quantitative traits such as cognitive or neurophysiological dysfunction. Such enriched syndromes or endophenotypes [48] may substantially increase the informativeness of patient samples for genetic and other biological research.

Reliability

Psychiatric research and communication among clinicians have long been impeded by the low reliability of diagnostic assessment and by the fact that key terms like schizophrenia were used in different ways in different countries, or even in different centres within a single country [49]. The situation has changed radically since the introduction of explicit or 'operational' diagnostic criteria in DSM-III [26] in 1980 and in the research version of ICD-10 [6] in 1993. DSM-III and its successors, as well as ICD-10, have undergone extensive field trials and their final versions have been shown to be highly reliable. It can be assumed that the diagnostic criteria of future classifications will be similarly field-tested to remove ambiguous elements in them, but it is unlikely that improving further the reliability of classification will remain a major goal – in contrast to issues of validity which now dominate the agenda. However, by and large, reliability imposes a ceiling on the evaluation of validity in the sense that validity would be extremely difficult to determine if the diagnostic category was unreliable [50].

Concepts of validity

If future versions of ICD and DSM are to be a significant improvement on their predecessors, it will be because the validity of the diagnostic concepts they incorporate has been enhanced. However, what exactly is meant by the validity of a diagnostic concept, or of a system of classification in psychiatry, is rarely discussed and few studies have addressed this question explicitly and directly. There is no simple measure of the validity of a diagnostic concept that is comparable to the established procedures for the assessment of reliability. Four types of validity are often mentioned in the discourse on psychiatric diagnosis – construct, content, concurrent and predictive – all of them being borrowed from psychometric theory

where they apply to the validation of psychological tests. A diagnostic category which: (i) is based on a coherent, explicit set of defining features (construct validity); (ii) has empirical referents, such as verifiable observations for establishing its presence (content validity); (iii) can be corroborated by independent procedures such as biological or psychological tests (concurrent validity); and (iv) predicts future course of illness or treatment response (predictive validity) is more likely to be useful than a category failing to meet these criteria. Few diagnostic concepts in psychiatry meet at present these criteria, and many of them are of uncertain applicability outside the setting in which they were generated [50].

Despite these ambiguities, a number of *procedures* have been proposed to enhance the validity of psychiatric diagnoses in the absence of a simple single measure. Robins and Guze [51] outlined a 'validation' programme with five components: (i) clinical description (symptomatology, demography and typical precipitants); (ii) laboratory studies (psychological tests, radiology and post mortem findings); (iii) delimitation from other disorders (by means of exclusion criteria); (iv) follow-up studies (including evidence of stability of diagnosis); and (v) family studies. Subsequently, Kendler [52] proposed to distinguish between antecedent validators (familial aggregation, premorbid personality, precipitating factors); concurrent validators (for example, psychological tests); and predictive validators (diagnostic consistency over time, rates of relapse and recovery, response to treatment). More recently, Andreasen [53] proposed 'a second structural program for validating psychiatric diagnosis' which includes additional validators such as molecular genetics and molecular biology, neurochemistry, neuroanatomy, neurophysiology and cognitive neuroscience.

The weakness of these procedural criteria is that they implicitly assume that psychiatric disorders are distinct entities, and that the role of the validating criteria and procedures is to determine whether a putative disorder is a valid entity in its own right or a variant of some other entity. The possibility that disorders might merge into one another with no valid boundary in between – what Sneath [54] called a 'point of rarity' – is rarely considered. In fact, several DSM/ICD disorders, such as bipolar affective disorder and depression, cluster non-randomly among the relatives of individuals with schizophrenia. Findings like these have given rise to the concepts of 'schizophrenia spectrum' and 'affective spectrum' disorders. It will not be surprising if such findings of overlapping genetic predisposition to seemingly unrelated disorders become the rule rather than the exception. It is equally likely that the same environmental factors contribute to the genesis of several different syndromes [55].

Predictive validity: course and outcome

Studies conducted over many decades consistently demonstrate that schizophrenia presents a spectrum of outcomes and course patterns, ranging from nearly

complete recovery after acute episodes of psychosis to continuous, unremitting illness leading to deterioration of cognitive performance and social functioning [56]. Between these extremes, a substantial proportion of patients show an episodic course with psychotic relapses and partial remissions during which affective and cognitive impairments become increasingly conspicuous and may progress to gross deficits. Although no less than one-third of all patients with schizophrenia have relatively benign outcomes, in the majority the illness still has a profound, lifelong impact on personal growth and development. The initial symptoms of the disorder are not strongly predictive of the pattern of course but the mode of onset (acute or insidious), the duration of illness prior to diagnosis and treatment, the presence or absence of substance use, as well as background variables such as premorbid adjustment, educational and occupational achievement, and availability of a supportive social network allow a reasonable accuracy of prediction in the short- to medium term (two to five years).

Longitudinal studies suggest that the characteristic symptoms of schizophrenia tend to 'breed true', that is, only a minority of patients are eventually reclassified into other disease categories because of a significant and lasting change in the predominant symptoms. Schneiderian 'first-rank' symptoms at first presentation, such as thought broadcast or insertion, passivity ('replacement of will') experiences and hallucinatory third-person 'voices' [24], which are given special diagnostic weight in both ICD-10 and DSM-IV, exhibited in the WHO 10-country study [1] a strong tendency to recur during subsequent psychotic episodes, but were not associated with a poorer outcome as compared to patients with no first-rank symptoms on initial examination.

The evidence that each of the 'classic' subtypes of schizophrenia is associated with a characteristic pattern of course is generally weak but surprisingly good for some of the subtypes. Consistent differences have been reported between paranoid, hebephrenic and undifferentiated schizophrenia (diagnosed according to DSM-III) on a long-term follow-up of 19 years [57]. Paranoid schizophrenia tended to have a remittent course, and to be associated with less disability, in contrast to hebephrenia which had an insidious onset and poor long-term prognosis. Undifferentiated schizophrenia occupied an intermediate position. In the WHO International Pilot Study of Schizophrenia [58], four alternative groupings of the ICD-9 subtypes were examined for differences with regard to several course and outcome measures. Clear discrimination was achieved between simple and hebephrenic schizophrenia grouped together, on the one hand, and the schizoaffective subtype on the other.

The course and outcome data on schizoaffective disorders seem to support their placement within the broad category of schizophrenia. A retrospective and prospective study of 150 schizoaffective patients and 95 bipolar affective patients [59] established general similarities between the two groups but the schizoaffective cases were less likely to achieve a full remission and more likely to develop a residual state. An intermediate outcome between that of schizophrenia and bipolar affective disorder is a common finding in schizoaffective disorders.

The current focus on early detection and treatment of first episodes of psychosis is supported by evidence suggesting that the course and outcome of the earliest stages of a schizophrenic illness may have a pathoplastic effect on its subsequent course. Specifically, the duration of untreated psychosis, (DUP) has been shown to correlate with prolonged time to remission and poor treatment response. [60,61].

What determines the long-term outcome of schizophrenic illnesses is far from clear but the stereotype view of the disorder as invariably progressive and leading to profound deterioration does not accord well with the evidence. In a significant proportion of cases, the disorder exhibits the features of a shift-like process with acute exacerbations and remissions which may progress to severe deterioration or come to a standstill at any stage. Whether a single underlying pathophysiology can explain the variety of clinical outcomes, or several different pathological processes are at work, remains obscure. It has been suggested that the longitudinal course of schizophrenia should be seen as an open-ended, dynamic life process with multiple, interacting biological and psychosocial determinants. Such issues cannot be resolved by clinical follow-up studies alone, and require a strong involvement of neurobiological research in prospective investigations of representative samples of cases spanning the entire spectrum of course and outcomes.

Criterion validity: genetics

The rapid advances in molecular genetics and genomics have given rise to expectations that genetic research will provide robust biological criteria for the validation (or refutation) of the current nosology of schizophrenia and its boundaries relative to other psychotic disorders. While this hope may ultimately come true, the present evidence is neither unequivocal nor consistent. In the light of recent findings, the genetic architecture of schizophrenia now appears to be far more complex than previously thought. In addition to the likely genetic heterogeneity of schizophrenia and other psychiatric disorders across and within populations, it appears possible that 'current nosology, now embodied in DSM-IV, although useful for other purposes, does not define phenotypes for genetic study' [62]. Most of the 'first generation' genetic linkage studies were predicated on the assumption that schizophrenia and bipolar disorder are 'natural' disease entities with distinct aetiology and pathogenesis, and that current diagnostic criteria, all the way from RDC and DSM-III to DSM-IV and ICD-10, identify 'real', biologically anchored phenotypes suitable for genetic analysis [63]. This assumption has failed to find unequivocal support from family, twin and population-based studies which often produce inconsistent or contradictory results [47]. On the one hand, a number of studies support the view that schizophrenia and bipolar disorder tend to 'breed true' in families and populations. In a large population-based sample from the Danish Psychiatric Register, most of the risk factors aggregating in families and previously reported to be associated with schizophrenia, were not found to be associated with bipolar

affective disorder, which supports at least a partial aetiological separation of the two disorders [64]. On the other hand, another population-wide study [65] linking a large number of Swedish pedigrees reported overlapping heritabilities and recurrent risks for schizophrenia and bipolar disorder, suggesting that the two disorders, at least in part, share common genetic causes.

The existence of a shared genetic susceptibility between schizophrenia and bipolar disorder has been further supported by results from 'second generation' genome-wide linkage and association studies. One of those studies [65] demonstrated that two candidate genes which had previously been implicated in schizophrenia, *DISC1* and *COMT,* map to regions on chromosomes 1q42 and 22q11 which were found to be significantly linked to both schizophrenia and bipolar disorder, suggesting that they may predispose to psychotic illness across the nosological schizophrenia-bipolar border. Similar findings of shared, trans-nosological effects have been reported for a number of other candidate genes, including *NRG1*, *DTNBP1*, *GRM4* and *G30/G72* [66]. Such findings have led to a proposal of a genetic susceptibility continuum spanning across schizophrenia and bipolar disorder and including, at its two extreme ends, unique genetic factors associated with each disorder and a middle zone of overlap, occupied by schizoaffective disorder and containing shared genetic factors [67]. This model was suggested as an alternative to the traditional nosology of the psychoses, replacing the 'Kraepelinian dichotomy'. However, it is extremely doubtful that the present state of knowledge about the genetic basis of schizophrenia and related disorders could provide a definitive evidence base for a meaningful revision of the classification of psychotic disorders.

First, the presence of shared genetic factors across complex disorders is neither a new discovery, nor is it limited to the schizophrenia – bipolar dichotomy. It is well known, for instance, that ischaemic heart disease and cerebrovascular disease share many risk factors and multiple susceptibility genes; yet such commonality has not led to their amalgamation into a single disease or a continuum because of the existence of specific differences in clinical symptoms, pathology, pathophysiology, and treatment. Complex disorders, such as schizophrenia, are likely to involve a very large number of genes operating in multiple functional networks, as well as significant interactions with the environment, including epigeneic effects [68]. This makes it extremely unlikely that a conceptually sound and practically useful classification of psychotic illnesses could be based solely on current genetic data.

Secondly, and more importantly, a real understanding of the genetic architecture of schizophrenia is at present simply lacking. It is important to realise that there are no simple linear relationships between specific genes and clinical, behavioural or cognitive outcomes. Genes do not specify particular symptoms or cognitive processes – they code for regulatory factors, signalling molecules, receptors and enzymes, which interact within complex networks, modulated by environmental influences. The concepts and technologies of molecular genetic and genomic research are evolving rapidly and, correspondingly, the views of the nature of the genetics underlying this group of disorders are likely to change dramatically in the

next decade, that is, long before the expiry of the useful shelf life of both DSM-V and ICD-11. Recent evidence supports a likely aetiological role for copy number variation (CNV), which includes rare, highly penetrant mutations in multiple genes, as well as a role for gene networks shared among schizophrenia, autism and certain forms of mental retardation [69]. Together with the prospect of cost-effective sequencing of entire individual genomes, these developments signal the emergence of a 'third generation' of genetic studies which are likely to have far-reaching implications for the future classification of psychotic disorders – especially if genomics is successfully linked with neural circuit analysis [70].

Aspects of culture

Current classifications tend to obscure the complex relationships between culture and mental disorder. Although both ICD-10 and DSM-IV acknowledge the existence of cultural variation in psychopathology, they essentially regard culture as a pathoplastic influence that distorts or otherwise modifies the presentation of the 'disorders' defined in the classification. Both systems ignore the existence of 'indigenous' languages in mental health [43] and this limits the relevance and value of the classification in many cultural settings. Although the essential syndromal structure of schizophrenia is discernible in quite varied cultural contexts [1,71], there are many instances of its difficult diagnostic differentiation from the so-called culture-bound syndromes or the variations in the expression of acute reactive psychoses in traditional societies and indigenous populations [72].

Reducing stigma

Countering the socially harmful negative stereotypes associated with the concept of schizophrenia should be an important objective of diagnostic classifications. The theory and practice of psychiatric diagnosis and classification cannot be divorced from their social context [73]. In the past this has rarely been a primary consideration in the development of classifications but there are good reasons to include 'stigma avoidance' among the criteria on which the merits of psychiatric classifications and nomenclatures should be assessed. The risk of misuse of diagnostic categories and classifications for political or economic purposes is not buried with the past. Misinterpretations of advances in neuroimaging and genetics in the form of simplistic determinism may again make psychiatry vulnerable to political ideologies, market forces and various forms of abuse. Concepts concerning the nature and classification of psychiatric illness and specifically schizophrenia will always attract ideological and political attention that can translate into laws or policies that may have unforeseen consequences for the human rights of patients suffering from the disorder.

REVISION OF THE CLASSIFICATIONS: PROSPECTS FOR SCHIZOPHRENIA

One classification or many?

For the last thirty years there have been two widely used classifications of mental disorders, the World Health Organisation's ICD and the American Psychiatric Association's DSM. Fundamentally, the two are similar, though there are some important conceptual differences, as well as differences in the definitions and diagnostic criteria for individual disorders. For a variety of reasons both classifications will continue to produce new editions or revisions and in some respects to compete with one another. It is, of course, uncomfortable to have two rival classifications, particularly as many of the differences between them are minor or accidental. On the other hand, the existence of two parallel classifications and diagnostic criteria does help to emphasise that most of the concepts of psychiatric disorders are still provisional and their definitions arbitrary. It is likely that the minor differences between the classifications will be reduced in future revisions, but where conceptual differences are involved, they should be explicated to stimulate research testing the advantages and disadvantages of the alternative concepts or definitions. Individual research groups may well produce novel concepts and definitions for specific purposes and should not be discouraged from doing so. Innovation is essential to progress and sooner or later radical changes are going to be needed [50].

CRITICAL ISSUES IN THE REVISION PROCESS

Disease or a broad syndrome?

Psychopathological syndromes are dynamic patterns of intercorrelated symptoms and signs that have a characteristic evolution over time. Although the range and number of aetiological factors that may give rise to psychiatric disorders is very wide, the range of psychopathological syndromes is limited. The syndromes of schizophrenia – paranoid, hebephrenic, schizoaffective, catatonic – to mention just a few – occur with impressive regularity in different individuals and settings, although in each case their presentation is imprinted by personality and cultural differences. Since a variety of aetiological factors may produce the same syndrome (heterogeneity) and conversely, a single aetiological factor may give rise to a spectrum of different syndromes (pleiotropy), the relationship between aetiology and clinical syndrome is an indirect one. In contrast, the relationship between the syndrome and the underlying pathophysiology, or specific brain dysfunction, is likely to be much closer. In the complex psychiatric disorders, where aetiology is multifactorial, future research into specific pathophysiological mechanisms could

be considerably facilitated by a sharper delineation of the syndromal status of many current diagnostic categories. In addition to their clinical utility, syndromes can also serve as a gateway to elucidating the pathogenesis of psychiatric disorders. This provides a strong rationale for reinstating the concept of the *syndrome* as the basic Axis I unit of future versions of psychiatric classifications.

'Deconstructing' schizophrenia: categories or dimensions?

Psychiatric classifications, such as DSM-IV and ICD-10, are eclectic in the sense that they are organised along several different classes of criteria (symptoms, behaviours or traits, age at onset, course and, occasionally, causes) without a clear-cut hierarchical arrangement among them. There are many different ways in which current classifications can be revised and modified, but one of the fundamental choices to be made is that between a categorical and a dimensional arrangement. It is worth recalling that, although most sciences start with a categorical classification of their subject matter, they often replace this with dimensions as more accurate measurement becomes possible [74].

Whether psychotic disorders can be better described dimensionally or categorically remains an open, researchable question [75]. The difficulties with dimensional models stem from their novelty; lack of agreement on the number and nature of the dimensions required to account adequately for clinically relevant variation; the absence of an established, empirically grounded metric for evaluating severity or change; and, perhaps most importantly, the complexity and cumbersomeness of dimensional models in everyday clinical practice.

These considerations seem to preclude, at least for the time being, a radical restructuring of psychiatric classification from a predominantly categorical to a predominantly dimensional model. However, if psychiatric classification ought to be eclectic and pragmatic, such restructuring may not be necessary or even desirable. Moreover, categorical and dimensional models need not be mutually exclusive, as demonstrated by so-called mixed or class-quantitative models [76] which combine qualitative categories with quantitative trait measurements. For example, there is increasing empirical evidence that should make it attractive to supplement a retained and refined categorical clinical description of the syndrome of schizophrenia with selected quantitative traits such as attention or memory dysfunction and volumetric deviance of cerebral structures.

Endophenotypes

Endophenotypes (intermediate, elementary, alternative, or correlated phenotypes) offer a novel approach to reducing the complexity and heterogeneity of schizophrenia that could provide either an alternative or a complement to symptom-based

phenotypes. As 'measurable components unseen by the unaided eye along the pathway between disease and distal genotype' [77], endophenotypes must meet criteria of being: (i) associated with the clinical disorder but not necessarily part of its diagnosis; (ii) heritable; (iii) state-independent (that is, present before the onset of active illness or during remissions); (iv) cosegregating with illness in families; and (v) found in unaffected family members at a higher rate than in the general population.

'Candidate' endophenotypes in schizophrenia research may include: (i) neurophysiological markers (for example, the P50 sensory gating potential, the P300 wave, antisaccade error rate, prepulse inhibition of the startle reflex); (ii) neuroimaging markers (for example, fronto-thalamic-cerebellar grey matter deficit, frontal hypoactivation in response to cognitive tasks); and (iii) cognitive markers (for example, continuous performance tasks, verbal memory deficit, prefrontal executive/working memory, spatial working memory). At present, the balance of the evidence suggests that cognitive dysfunction meets most of the criteria of an endophenotype in schizophrenia. This conclusion is underscored by the meta-analysis by Heinrichs and Zakzanis [78] of 204 studies published between 1980 and 1994 (a total of 7,420 schizophrenia patients and 5,865 controls), in which effect sizes (Cohen's *d)* and the U statistic (degree of non-overlap) were calculated for 22 neurocognitive test variables ranging from IQ, verbal memory and attention to executive function and language. Neurocognitive deficit was found to be a reliable and well replicated finding in schizophrenia. The dissection of the schizophrenia syndrome into modular endophenotypes with specific neurocognitive or neurophysiological underpinnings is beginning to be perceived as a promising approach in schizophrenia genetics. The study of endophenotypes cutting across the conventional diagnostic boundaries may reveal unexpected patterns of associations with symptoms, personality traits, or behaviour which may in the future substantially recast the psychiatric nosology [63].

The concept of utility

Most contemporary psychiatric disorders, even those like schizophrenia with a pedigree stretching back to the nineteenth century, cannot yet be described as valid disease categories. This does not mean, though, that they are not valuable concepts, and it is crucial to maintain a clear distinction between validity and utility. Kendell and Jablensky [50] proposed that a diagnostic rubric may be said to possess utility if it can be shown to provide non-trivial information about prognosis and likely treatment outcomes, and/or testable propositions about biological and social correlates. The term utility was first used in the sense proposed by Meehl (79) who wrote that 'the fundamental argument for the utility of formal diagnosis ... amounts to the same kind of thing one would say in defending formal diagnosis in organic medicine. One holds that there is a sufficient amount of aetiological and

prognostic homogeneity among patients belonging to a given diagnostic group so that the assignment of a patient to this group has probability implications which it is clinically unsound to ignore'.

Many, though not all, of the diagnostic concepts represented by the categories of disorder listed in contemporary nomenclatures like DSM-IV and ICD10 are extremely useful to practicing clinicians, and most clinicians would be hard put to cope without them. Diagnostic categories provide invaluable information about the likelihood of future recovery, relapse, deterioration and social handicap; they are often essential for decisions about treatment; and they provide a wealth of information about similar patients encountered in clinical populations or community surveys throughout the world – their frequency and demographic characteristics, their family backgrounds and pre-morbid personalities, their symptomatology and its evolution over time; the results of clinical trials of several alternative therapies; and research into the aetiology of the syndrome. This is all useful and sometimes invaluable information whether or not the category in question is valid. How useful it is depends mainly on two things: the quantity and quality of the information available in the literature, which will depend on how long the category has been recognised and provided with adequate diagnostic criteria, and how much competent research it has generated; and how different the implications of that information, particularly about aetiology, prognosis and treatment, are from the implications of analogous information about other related syndromes. The DSM-IV definition of schizophrenia, for example, is particularly useful for predicting outcome, largely because some degree of chronicity is in-built. But a much broader definition, embracing a heterogeneous 'schizophrenia spectrum', may be more useful for defining a syndrome with high heritability [50].

CONCLUSION

It is important to maintain awareness of the fact that most of psychiatry's disease concepts are merely working hypotheses and their diagnostic criteria provisional. The protagonist of modern psychiatric nosology Emil Kraepelin wrote, late in his career, that 'it is now necessary to turn away from arranging illnesses in orderly, well defined groups and to set ourselves instead the undoubtedly higher and more satisfying goal of understanding their essential structure' [14].

Nine decades later, both the arrangement of psychiatric disorders and the understanding of their essential structure is an unending quest, despite spectacular advances in neuroscience, genetics and therapeutics. The basic construct underlying current psychiatric classifications remains that of nosological entity, retained in modern psychiatry more or less in the form in which it was first formulated by Kahlbaum (1874) and elaborated by Kraepelin, postulating correspondences between clinical symptoms, course, brain pathology and aetiology as criteria defining a 'natural disease entity'. In actual practice, the validating criteria remained

restricted to the cohesion of the clinical picture and disease outcome as a proxy for brain pathology.

Today, both DSM-IV and ICD-10 are essentially classifications of diagnostic concepts, and not of 'natural kinds', such as people or diseases. Despite historical and recent assumptions to the contrary, there is little evidence that most currently recognised mental disorders are separated by natural boundaries. Diagnostic categories defined by their syndromes should be regarded as valid only if they have been shown to be discrete entities with natural boundaries separating them from other disorders. Most diagnostic concepts in psychiatry have not been shown to be valid in this sense, though many possess utility by virtue of the information about outcome, treatment response and aetiology which they convey. Researchers are increasingly assuming that variation in symptomatology is continuous and therefore questioning the validity of contemporary classifications. Although the evidence is far from being consistent or definitive, there is a growing understanding that the broad syndromal spectrum of schizophrenia, a complex disorder comprising multimodal cortical abnormalities and cognitive dysfunctions with or without frank psychotic manifestations, is the end-point phenotype for heterogeneous gene networks, pathophysiological pathways and environmental modifiers.

Recent proposals to deal with biological heterogeneity by linking genomics with neural circuitry analyses that may cut across conventional disease categories [70] resonate – surprisingly – with Kraepelin's late views on pre-existing response templates of the human brain and 'registers' of continuous variation replacing the 'natural disease entity' concept.

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