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POINTS OF VIEW/FORMULATION

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Systematic of psychiatric disorders between categorical and dimensional approaches

Kraepelin's dichotomy and beyond

Abstract This paper describes basic principles of systematics for psychiatric disorders such as the categorical and dimensional approach. It summarises validity aspects of the traditional psychiatric nosology and syndromatology. The importance and limitations of the dichotomy of schizophrenia and affective disorders, first suggested by Kraepelin, is reviewed in the light of results from modern research in the field of classification, follow-up and neurobiological studies, especially neurochemical, neurogenetic and neuroimaging studies. Current developments towards DSM-V and ICD-11 are critically reflected. The conclusion is reached that there might be insufficient data to establish a new systematics of psychoses. Therefore it might be premature to leave the Kraepelinian dichotomy totally although it has to be modified in the light of new research.

Key words systematics of psychiatric disorders · classification · syndromatology · dimensional approach · categorical approach · Kraepelin dichotomy

Introduction

Like every branch of science, psychiatry attempts to give specialised terms to the phenomena of its area of research, and to classify them according to various aspects. Such classification allows systematic investigation, communication and comparison of the results of observations. The specialised terms used in this process, abbreviations for more or less complex facts or constructs, should be defined as accurately as possible to guarantee optimal scientific communication [190, 194, 199]. Classification means two things:

(a) Firstly, the subdivision of diversity (various characteristics, populations of cases) into a system ordered according to classes (classification). The term 'classes' describes an entirety of elements with common characteristics.
(b) Secondly, the assignment of individual characteristics or cases to the classes of such a system (diagnosis).

This paper will describe some principal problems in the systematic ordering of mental disorders, advantages and disadvantages of either a nosological/categorical or syndromatological/dimensional system, reliability and validity aspects of diagnostic entities in the traditional and current psychiatric classifications and the future development of the definition and systematics of psychiatric disorders. In this context, the classification of non-organic psychoses, in particular the dichotomy between schizophrenic and affective psychoses as originally suggested by Kraepelin, will be focussed on as an example of dilemmas in the classification of psychiatric disorders.

Basic problems in the classification of mental disorders

Logical classifications are characterised by precise stipulation of the characteristics or combinations of characteristics that define the individual classes, whereby the reasons for classification are retained (the criterion according to which the classification was made). All phenomena that occur in the area of evaluation are considered, and inclusion and exclusion criteria for assignment of individual cases to classes are defined. Most empirical classifications do not achieve the criteria valid for logical classifications [139, 218, 219]. This is related on the one hand to the complexity of phenomena in real patients, which can only be assigned to classes by different kinds of abstractions, and on the other hand to the fact that empirical classification normally attempts to form classes not only based on external character-

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istics, but also to use postulated or proved conformances as characteristics for classification and thus to create a 'natural' system as opposed to an 'artificial' system.

If one considers the complexity of the appearance of mental disorders, the continuity between the various types and the insufficient knowledge about the way they originated, most of what has been said about the difficulties associated with the classification of mental disorders becomes understandable. This is particularly true for attempts at classification in which not only the temporal cross-section of symptoms, but also assumptions about causal factors, the spontaneous course and the response to certain therapeutic procedures serve as criteria for classification. However, it is precisely these theoretical factors that are of great relevance for the classification of mental disorders, as for all classifications [22]. Numerous classification criteria and, therefore, varying classifications are readily conceivable, e.g. aetiopathogenesis, phenotype, course, therapeutic response, etc. Different classifications result, depending on the criteria chosen (e.g. Kraepelin's nosological system or that of the Kleist–Leonhard school), sometimes with different levels of abstraction (syndromatology, nosology). The classes thus formed represent the result of an idealising abstraction and selection process. They do not correspond with entities that really exist, but are theoretical terms [194] or constructs [190] and therefore depend on the respective theoretical position. This point of view, together with the fact that there are smooth transitions between the various classes, comes closest to doing justice to the interpretation that the classification of mental disorders is basically a typology [293]. 'Types' include all characteristics on which the similarities between the objects belonging to them depend on, even if some or even most of these objects do not show every characteristic that constitutes the type. Types do not really exist, but arise through abstraction of real facts. They represent a sort of 'original form' around which the real objects vary in the configuration of their individual characteristics. Due to their own blurred definition, conceptions of types have a broader field of application than conceptions of classes. This is because they also do justice to ranges of objects in which unclear borders between different phenomena make a clear separation into individual classes more difficult or even impossible. Under this aspect, typological classifications of mental disorders appear principally to be more suitable than categorical classifications. In the context of a typological approach one can differentiate between 'extreme' and 'accumulation' types. Extreme types are the extremes of a normal series of variations, e.g. mental retardation as an extreme variation of the normal distribution of intelligence. Accumulation types are centres of accumulation of variable forms of pathological behaviour patterns, such as the subtypes of schizophrenia or the different exogenous reaction types (acute exogenous psychoses), for example.

Besides classification into classes or types, as is characteristic particularly for the nosological classifications of psychiatry, it is possible to classify mental disorders on a dimensional basis [85, 86, 134]. In the most simple case such a system is one-dimensional in as it simply contains a continuum from optimal psychosocial adaptation through to the most severe degrees of psychosocial disintegration [94, 99]. On the other hand, multidimensional systems are mostly based on concepts of variations of several character traits or behavioural patterns. Eysenck [86] in particular propagated the dimensional classification of mental disorders, based on behavioural theoretical conceptions and the results of multivariate statistical analyses of questionnaires on personality traits. In this case the phenomena are arranged in a continuum that is characterised by certain dimensions-Eysenck proposed neuroticism, psychoticism and introversion/extroversion. Eysenck's basic assumption that dimensional rather than classificatory systematics apply to the real conditions, since there is no basic difference between the characteristics of healthy and pathological behaviour, is not undisputed [139]. This conception may apply to personality disorders and oligophrenias, but at least for the psychoses one can expect deviations from the norm in which on the one hand qualitatively novel elements beyond the normal range of events occur (e.g. hallucinatory perceptions) and on the other hand an abnormal combination of normal characteristics [296]. Independent of the question whether dimensional, categorical or typological classification of mental disorders better corresponds to the real situation, any dimensional systematics becomes categorical or typological if certain degrees of expression of certain behavioural patterns are rated as 'mentally healthy' or 'mentally ill', or as diagnostically, therapeutically or prognostically relevant, on the basis of statistical averages. The main types of psychopathological phenomena are then rated as extremes (extreme types) of certain characteristic traits or behavioural patterns. To use an example, Eysenck's systematics, which attempts to portray the main types of psychopathological phenomena as extreme variations of normal personality traits, characterises hysteria as a combination of extreme neurotic tendencies with extraversion, and schizophrenia as a combination of extreme psychoticism with neurotic tendencies and introversion.

In order for a systematics of mental disorders to serve as a useful basis for decisions and interventions, at least the following criteria must be fulfilled:

(a) The systematics must enable optimal prognoses about the spontaneous course and therapeutic response to be made.
(b) It must enable conclusions to be drawn about possible causal factors.

(c) It must enable individual cases to be assigned reliably.

The better a classification of mental disorders fulfils these criteria, the better it is suited to everyday clinical practice [207].

Some evidence aspects for a syndromatological systematics

A syndromatological systematics can be either dimensional or categorical. A purely dimensional approach describes the expression of certain behavioural patterns on a psychometric continuum in one or several predefined dimension. Each individual can be diagnosed precisely according to his individual behaviour pattern. A dimensional systematics can be transduced into a categorical one if certain score values are defined as acutely ill or as diagnostically, prognostically or therapeutically relevant.

The same is true if only the existence of a syndrome, without a psychometric characterisation, is used for classification purposes. Such a simple, syndromatological systematics based on global clinical judgment, not on a differentiated psychometric approach, was proposed as early as Kraepelin's day by his opponent, Hoche [118], who questioned the validity of the Kraepelinian classification. Clinicians are still interested in using such a simple syndromatological approach without assessing the distribution of certain behavioural pattern in a dimensional way using a psychometric assessment.

The syndromatological approach is either seen as an alternative or addition to a nosological classification. The interest in a syndromatological approach was reviewed in the context of criticism about the validity and reliability problems of nosological psychiatric classification [64, 67], and in particular in the context of the development of psychopharmacology, which in the opinion of many experts is orientated rather towards syndromes than nosological entities [191, 270].

The syndromatology of mental disorders arose primarily on the basis of clinical intuition. It describes the joint appearance of symptoms without considering the conditions of their origins. It is a common understanding that psychopathological syndromes are generally unspecific with respect to the aetiopathogenetic factors on which they are based: the same syndromes may have different causes, and the same causes can result in different syndromes [295]. However, there are certain global associations, for example that psychoses with a somatic cause mostly appear as acute exogenous reactions types or chronic organic brain syndrome [33, 130].

Statistical methods to investigate the accumulated joint occurrence of single symptoms are the factor and cluster analyses. The data on which evaluations performed with these methods of multivariate statistics are obtained from psychopathological findings recorded with rating scales [212, 213]. When taken together, such evaluations, performed with different rating scales in different patient samples and countries, resulted time and again in similar group factors or symptom clusters, and the assignment of the symptoms to syndromes proved to be relatively stable [23, 48, 149, 163, 216, 227]. The syndromes ascertained with multivariate statistical methods correspond to some of the traditional syndromes that arose on the basis of clinical intuition, e.g. paranoid-hallucinatory, manic, depressive, apathetic, hypochondriac, phobic-anancastic and mnemic syndromes [217]. These syndromes can therefore be seen as empirically confirmed, if one assumes that the term 'clinical syndrome' also means the accumulated joint occurrence of single symptoms. Inclusion of a larger variety of psychopathological states, in particular those with a somatic cause or of the neurotic kind [188], would probably confirm further clinically described symptoms. The factor emotional instability described by Eysenck [86] and other authors as 'neuroticism', seems to be relevant for neurotic disorders since it obviously differentiates between healthy subjects and neurotics [63, 87, 273].

A complex syndromatological classification of cases not only referring to one syndrome can be achieved on the basis of multivariate statistical analyses of patient samples by combining several syndromes, each of a certain degree of expression, to typical syndrome profiles. Such syndrome profiles allow one to form diagnostic groups, under consideration of the similarity of the profiles and without considering the clinical diagnosis. This was demonstrated among others by Lorr [162], using endogenous psychoses as an example. These typical syndrome profiles may correspond to known diagnoses. However, if this is not the case, it usually remains unclear what should be done with the newly found diagnostic types. Earlier attempts to form a new kind of classification based on this have not been realised on a larger scale [219]. Instead, the opposite path was followed, i.e. average profiles for each diagnosis group were empirically ascertained on the basis of clinical diagnoses [23, 98, 211, 217]. In principle, this procedure can also be applied at the symptom level, although a frequency analysis is normally performed here [79, 217, 234]. The utilisation of average profiles facilitates the psychopathological comparison and syndromatological or nosological assignment of patient groups as well as the course analysis of single case evaluations and group statistical evaluations and improves their information content [198, 220, 280] (Fig. 1). Furthermore, syndromes based on psychometric assessment give rise to new prognostic possibilities [214, 215, 283].

A syndromatological classification with syndrome profiles on the basis of rating scales appears to be

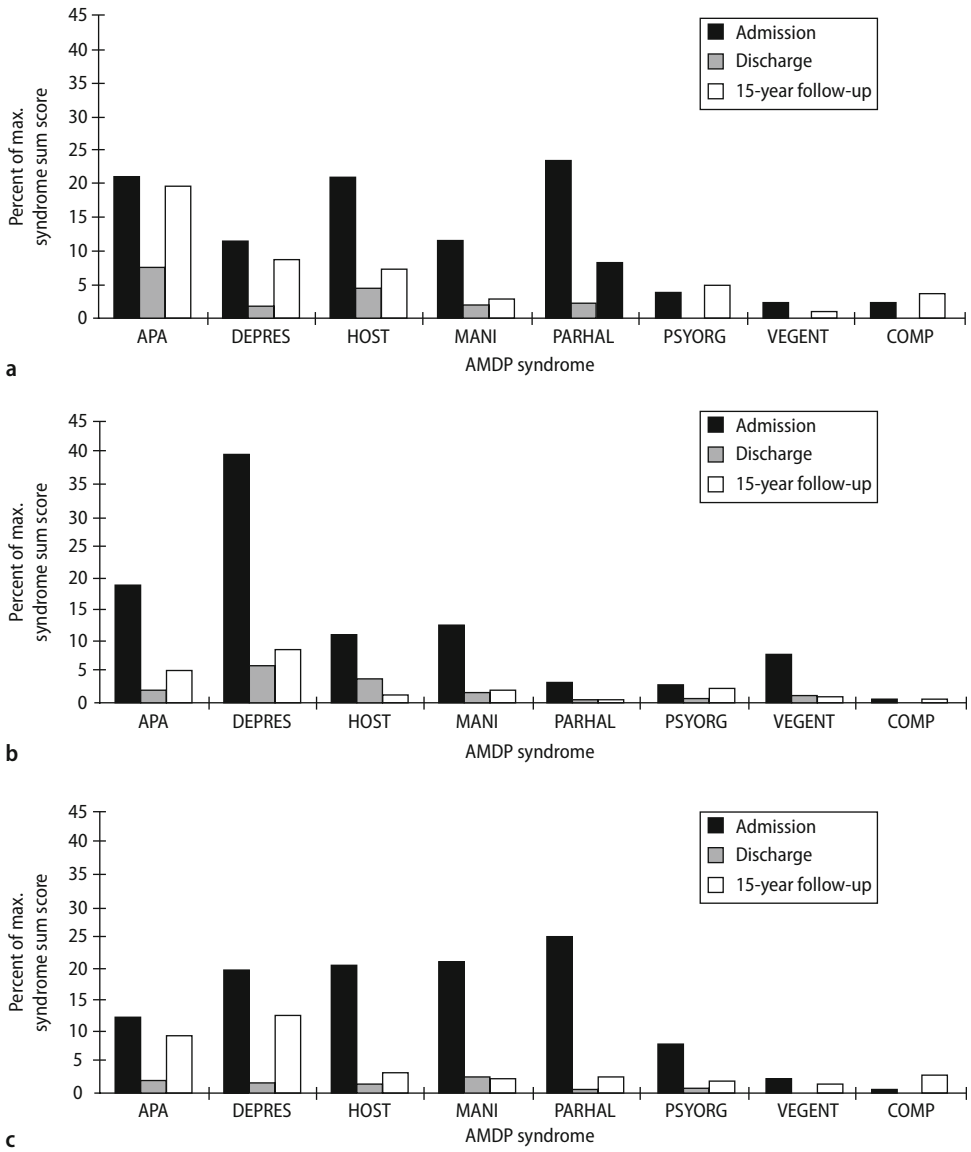

Fig. 1 Course of association for methodology and documentation in psychiatry (AMDP) syndromes [203]. **a** Schizophrenic disorders; **b** affective disorders; **c** schizoaffective disorders. *APA* apathetic syndrome; *Depres* depressive syndrome; *HOST* hostility syndrome; *MANI* manic syndrome; *PARHAL* paranoid-hallucinatory syndrome; *PSYORG* psychoorganic syndrome; *VEGET* vegetative syndrome; *COMP* compulsive syndrome

advantageous for various reasons: development of more precise diagnostic algorithms, greater reliability, greater ability to differentiate through quantifying presentation of syndrome profiles. However, just related to symptom patterns, a syndromatological classification cannot completely replace a nosological classification since it does not consider aetiology, course and therapeutic response. Under this aspect the diagnosis of a syndrome is only rarely used as a final diagnosis but rather as a reliable step on the way to a nosological diagnosis or as dimensional subtypology in the context of a preliminary categorical system.

In order to study the genesis of a syndrome, information has to be collected about the biography, primary personality, influence of noxious substances, causal biological factors, etc. This approach led to the concept of the 'final common pathway' that leads from the multiple conditioning factors to the uniform clinical syndrome [295]. If one also includes information about therapeutic response in such an analysis [231], the disadvantages of a syndromatological classification described above no longer apply and one obtains a new type of nosological systematic.

It was questioned whether even syndromes are too complex and not meaningful entities when researchers want to find associations e.g. with causal neurobiological parameters (270, see also the contribution of Praag in this supplement!). This might be principally meaningful from the perspective of neurobiological research, but could also lead to complications e.g. in terms of reduced interrater reliability on the symptom compared to the syndrome level. Also, an increasing risk for statistical findings by chance given the high number of symptoms in patients having a certain disease, when all symptoms are correlated with a neurobiological parameter, should be considered. Keeping in mind that van Praag's 'functional psychopathology' focuses primarily on the serotonin

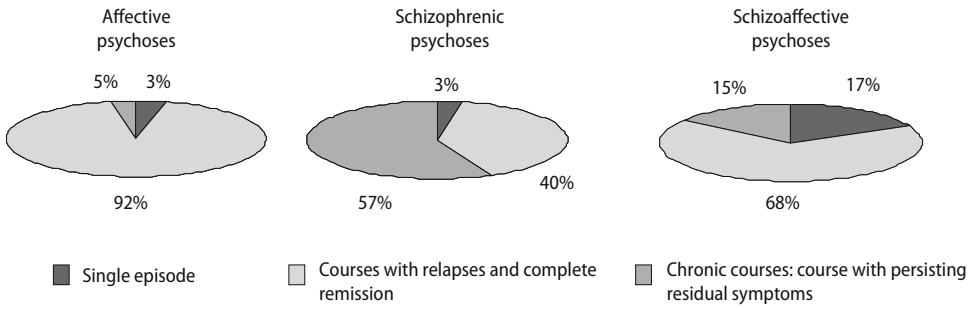

Fig. 2 Munich 15-year follow-up study: course of schizophrenic, affective and schizoaffective psychoses (ICD-10) [195]

system, associating with disturbances of this system with obsessive-compulsive symptoms, aggression, etc, it should also be considered that the neurobiological causation of symptoms is often complex and involves more than one transmitter system. For example, recent research has demonstrated that obsessive compulsive symptoms are apparently not only associated with disturbance of the serotonergic system but that disturbances of the dopamine system might also be involved. The proposal of a 'modular system' of psychopathology (Gaebel—see contribution in this supplement) has some similarities with the 'functional psychopathology', but it focuses not on transmitter systems but on neurophysiological/neuropsychological concepts. It has to be further investigated whether it can fulfil the aim to give an improved explanatory and classificatory approach. Recently also from a genetic approach it was tried to find associatives between genetic alterations and symptoms/syndromes. The findings focussed on the 72 gene. Interestingly three research groups found three totally different associations [102, 256, 279]. This underlines that associations on a genetic basis with clinical symptoms/syndromes might not be easier to find than associations with higher disorder entities. If one tries to understand the relationship between genes and clinical phenotypes on the disorder or syndromatic level this seems not to astonishing. A gene modulating different (neuro-) biological functions which finally can have an impact on the causation of different syndromes/symptoms depending on the function which are modulated [61].

There is some hope that endophenotypes, which in contrast to symptoms are more stable and persistent, could be better targets for associations with disorders or syndromes [51, 155, 164, 266].

Some evidence aspects for a nosological classification

In addition to symptoms, the nosological classification of mental disorders considers the course and response to therapeutic procedures and, if known, the aetiology and pathogenesis of the symptoms. Owing to the greater complexity which results from the inclusion of so many factors, particularly known and suspected aetiopathological factors, there are significantly more divergent attempts at classification than in the area of syndromatology [294].

The nosological classifications commonly used in psychiatry today are based to a great extent on the classification designed by Kraepelin, which stemmed from clinical intuition [149] and still seem to have some validity, at least as far as outcome is concerned (Fig. 2, see Chap. 6). On the basis of ideas from Griesinger [106] and nosological descriptions from several eminent psychiatrics of the nineteenth century like Hecker and Kahlbaum, Kraepelin tried to draw up 'disorder units' and unite them into one system by considering simultaneously the overall cross-sectional and longitudinal clinical pictures and the degree to which they could be influenced therapeutically, together with the anatomical and aetiological pathological basis. Kraepelin categorised the main groups of disorders according to causal factors, most of which, however, were hypothetical, and some of which still are. Bonhoeffer's discovery [33] that different somatic causes can give rise to the same psychopathological symptoms, and that the same cause can give rise to various psychopathological symptoms, was the basis for subsequent fundamental criticism of Kraepelin's nosology. However, the basic features of his nosology, especially the dichotomy between dementia praecox (later called schizophrenia by E. Bleuler) and manic depressive disorders, still became accepted worldwide (Fig. 3) and are still accepted to this day. Nevertheless, the dichotomy is facing increasing criticism based on the results of modern research, especially genetic research [67]. The non-specificity of mental disorders with respect to the causal factors was and still is interpreted as a result of interference by several factors relevant for aetiopathology (genetic disposition, primary personality, biography, poisons, etc.) [26, 128]. In this context one refers to the multiconditionality of mental disorders.

Not only was the basic conception of Kraepelin's 'disorder units' repeatedly questioned [139], but there were also critics of his special nosological classification. The critics either favoured the one extreme of a pooling of the generally differentiated types schizophrenia, manic-depressive disorder and schizoaffective disorder as an 'Einheitspsychose' [106, 240] or, more recently, a 'continuum of psychoses' [71–74], or

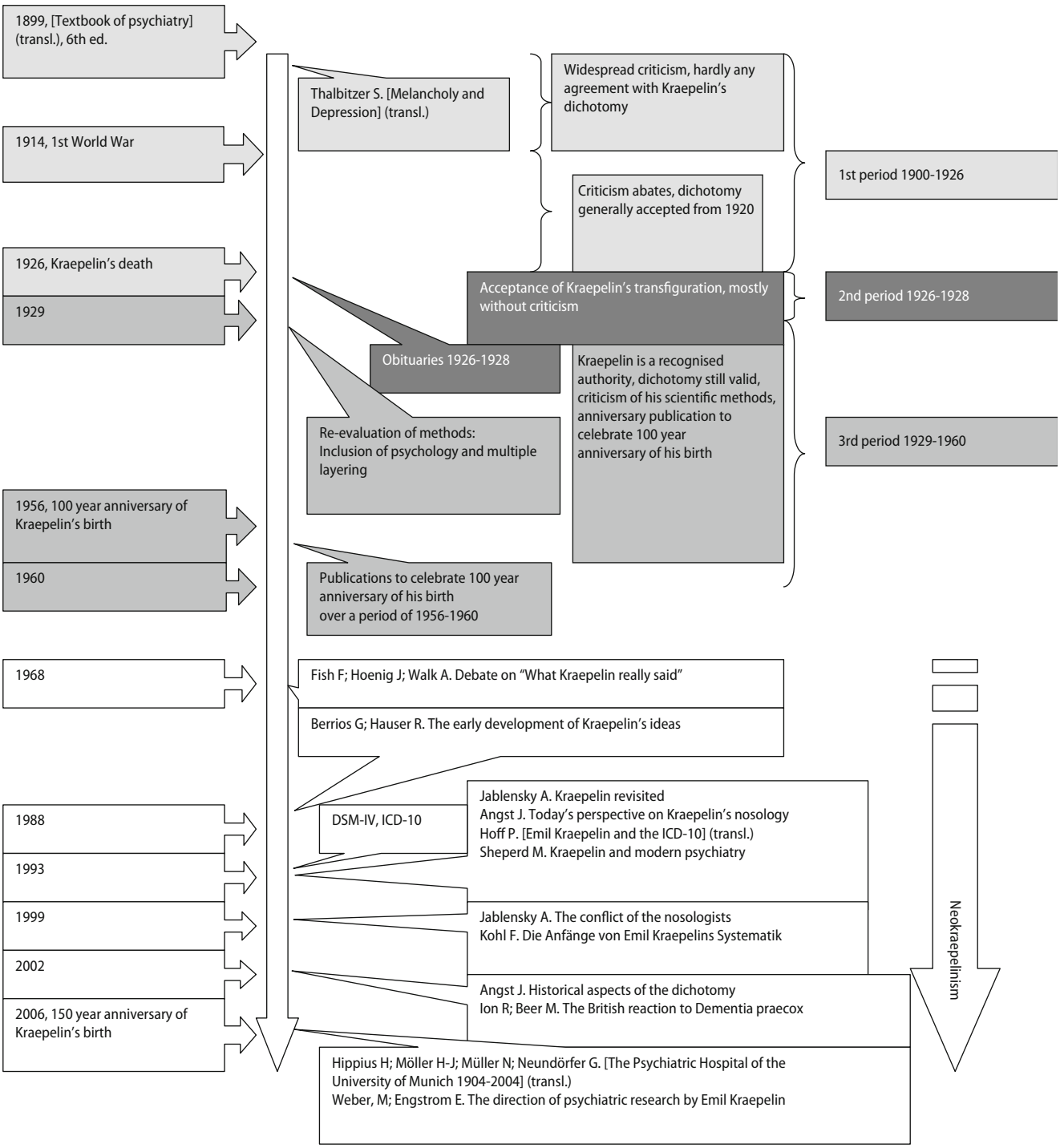

Fig. 3 The reception of Kraepelins work (U. Palm unpublished Data, Munich)

propagated the other extreme of their dissolution into numerous special forms according to family genetics, symptoms and course [157]. However, modern twin and family genetic studies, as well as studies of course and neuropathology, give insufficient support to the concept of a uniform psychosis since affective psychoses can be differentiated from schizophrenic psychoses at least to a certain degree with respect to genetic aspects, brain neuropathology and the course of the disorders [16, 58, 114, 166, 168, 177, 178, 180, 182, 187, 202, 209, 226, 237, 257, 267]. The categorisation between schizophrenia and affective psychoses and the differentiation of the other diagnostic entities might therefore not fully reach the demands for a clear-cut categorical systematics, at least there might be reasons enough to continue with these concepts at

least in a typological sense. However, many experts, especially from the field of basic science, currently find it more interesting to omit these diagnostic entities and develop a new systematics, primarily based on parameters of basic science than on clinical observations (see Chap. 8), although the 'point of rarity' as an indicator for a categorical/typological differentiation [138, 141] in the distribution of relevant symptoms or other variables might be missing. With respect to further differentiation, the concept of schizoaffective psychoses [41, 131] as a special type between schizophrenic and affective psychoses is generally seen to be supported by some family genetic and catamnestic findings [14, 177, 182, 202, 267]. The differentiation between unipolar depression and bipolar (manic-depressive) psychoses can be seen to be established on the basis of empirical findings [12, 15, 17, 176].

Evaluations of the different responses of various disorders to certain types of treatment [54, 191, 254] appeared to justify for a long time the traditional syndromatology and partly also the psychiatric nosology, at least as far as the rough classification was concerned, e.g. lithium is preliminary effective for prophylaxis in affective and schizoaffective psychoses; electroconvulsive therapy is very effective for 'endogenous' (major depressive disorder) but not for "neurotic" depression (dysthymia); traditional neuroleptics mainly influence the symptoms of schizophrenic psychoses but not depression to a similar degree. However, this has to be viewed more critically in light of modern developments in psychopharmacology where SSRI antidepressants, for example, have not only demonstrated efficacy in depression but also in anxiety disorders [21, 272], and second generation antipsychotics have shown efficacy not only in treating psychotic but also depressive symptoms of schizophrenic patients and even in acute bipolar as well as unipolar depression (Fig. 4) [196, 197]. Thus, response to psychopharmacological treatment does not seem suitable for generating or validating a classification of psychiatric disorders (Table 1).

The application of statistical procedures, particularly of the multivariate kind, opened up new possibilities for the consolidation, extension and revision of traditional nosological conceptions. This research started as early as the 1970s. Not only were data from psychopathological parameters used, but also anamnestic, somatological and other data. For example, Everitt et al. [84] used cluster analyses to divide a population of psychiatric patients into four groups with the diagnoses mania, depressive phase of a manic-depressive psychosis, acute paranoid schizophrenia and chronic schizophrenia. Roth et al. [241] used multivariate statistical analyses of the symptoms of patients with affective disorders to differentiate them into three symptom groups, which corresponded to the diagnoses endogenous depression, neurotic depression and anxiety neurosis. Paykel [231] included in the multivariate statistical analysis

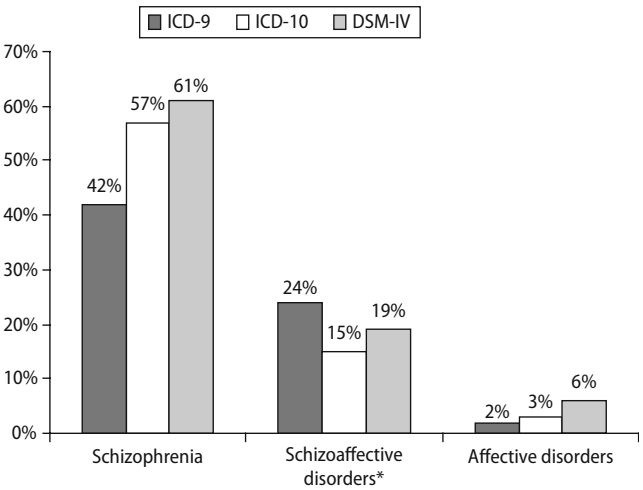

Fig. 4 Munich follow-up study: relative proportion of chronic courses in the diagnostic groups in ICD-9, ICD-10 and DSM-IV. *Including reactive, acute transient and Schizophrenigram disorders

of his patient sample not only data about symptomatology but also information about life events, premorbid personality and therapeutic response, and thus compiled a classification of the non-psychotic depressions into neurotic depression and non-psychotic chronic depressive reaction. A modern variant of this kind of classification research in the field of depression is the work by Parker et al. [228–230]. On the basis of statistical analyses of the symptomatology in various patient samples, several authors investigated the frequency of occurrence of transitional forms between the nosological types [54, 142]. This work was continued up to modern research on classification of psychoses, which focussed especially on the concept of schizoaffective psychoses [3, 123, 174, 175, 182] as well as on the acute reactive/polymorphic psychoses [126, 175, 197]. The results of these investigations were partially inconsistent. Nevertheless, altogether the indications for the validity of traditional nosology on this level of symptomatology and outcome, at least in its rough definition, e.g. the Kraepelin dichotomy, seem to prevail.

Psychiatrists usually tend to assume that a nosological diagnosis includes more information and as a

Table 1 Psychopharmacological decision-making and psychiatric classification

1. *Nosological* e.g. treatment of schizophrenia with antipsychotics (supposed main mechanism: antidopaminergic)
2. *Syndromatological* e.g. treatment of psychotic symptoms with antipsychotics, treatment of depressive symptoms in the context of schizophrenia with antidepressants
3. *Transnosological* (*trans-syndromal*?) Antidepressants (especially SSRIs) not only for the treatment of depressive but also anxiety disorders (supposed main mechanism: serotonergic/noradrenergic)
4. *Based on pharmacological mechanisms* e.g. second generation antipsychotics with their broad spectrum of pharmacological mechanisms can be used
- To treat schizophrenia (antidopaminergic action: D2/D3 blockade)
- To treat depression (serotonergic action: 5HT2 blockade, 5HT1 agonism)
- To treat anxiety disorders? (serotonergic action)

Table 2 Schizophrenic disorders according to ICD-10 and DSM-IV

ICD-10	DSM-IV
• Delusions of control/influence, delusional perception • Hallucinations, especially commentary or voices conversing with each other • Thought broadcasting/insertion/withdrawal, delusions of power or ability, incoherence, breaks in train of thought, etc. • Catatonic symptoms • Negative symptoms such as apathy, paucity of speech, flat affect • Characteristic symptoms present for at least 1 month • No detectable organic cause	• Delusions, especially bizarre delusions • Hallucinations, especially commentary or voices conversing with each other • Incoherence • Catatonic symptoms • Flat affect, avolition, social withdrawal • Worsening of social adaptation • Signs of disorder present for at least 6 continuous months • No detectable organic cause

ICD-10 and DSM-IV define a catalogue of criteria for the diagnosis of schizophrenia. This chart shows a modified version fo the catalogue with the aim of demonstrating that despite differences in details, there are large areas of overlap between the two classification systems

consequence also has more predictive power than a syndromatological diagnosis. However, recent findings demonstrated that the categorical differentiation between schizophrenic and affective psychosis was not of better predictive value for long-term outcome, and even that a prediction based merely on syndromes or the syndromatological approach was superior [124, 268, 269]. In this context, the study by Allardyce et al. [6] is also of interest since it demonstrated different patterns of association between either categorical diagnoses or dimensional representations of known risk factors for psychosis.

The development of DSM III/IV and ICD 10

Several steps were undertaken in the last two decades to achieve a further improvement of nosological categorical diagnoses and standardisation of psychiatric diagnostics.

An improved standardisation of diagnostic categories can be achieved by defining clear inclusion and exclusion criteria for every diagnosis according to the following principle: in order to make diagnosis D, the patient must present with Symptom A together with one of the symptoms from the series B, C and E, but symptoms P and O may not be present (Table 2). The so-called Feighner criteria [89] proceed according to this principle, as well as the research diagnostic criteria (RDC) [260], which are a further development of the Feighner criteria and the DSM-III [7] and which, in contrast to the other two systems, allow all psychiatric disorders to be diagnosed. It could be shown that merely the application of the RDC resulted in a significant improvement of the psychiatric diagnoses compared to a categorisation based on definitions in the DSM-III, and that the reliability scores could be even further improved if the related standardised rating instrument, the schedule for affective disorders and schizophrenia (SADS) [165, 259, 260], developed by the same working group, was applied. The interrater reliability for all diagnoses had a Kappa score higher than 0.75. In order to allow the DSM-III to be applied for routine diagnoses, inclusion and exclusion criteria had to be modified from those in the RDC to give greater flexibility since otherwise too large a percentage of patients could not be categorised. The fear that the precision required for scientific purposes of categorisation would suffer from the greater flexibility was unfounded in the face of several large interrater reliability studies with DSM-III [261]. DSM-IV [9] followed this approach, while ICD-10 developed two different systems, a less rigid one, the clinical diagnostic guidelines for routine care [289] and a version using stricter operationalizations, the research criteria for scientific purposes [291].

The diagnostic and statistical manual of mental disorders (DSM-III; American Psychiatric Association [7], was introduced by the American Psychiatric Association in 1980, and was partially conceived according to different classificatory criteria. Many of its definitions of various disorders no longer corresponded to the ICD-9 (compare, for example, the DSM-III and ICD-9 diagnoses of schizophrenia [221]). These changes were partially a consequence of the fact that certain 'poor compromises' had to be made based on the desire for international standardisation. Furthermore, they were supposed to better represent the current level of empirical knowledge.

In the DSM-III, the individual diagnoses are defined by short clinical descriptions of the clinical picture and through operationalised diagnostic criteria (see below). In addition, in the DSM-III a so-called multiaxial classification with five axes was introduced, which was supposed to allow various areas of information relevant for prognosis and therapy to be recorded separately. The first axis serves to record the current psychopathological disorder (syndrome diagnosis), the second a personality disorder. On the third axis, physical disorders relevant for the aetiology or treatment of the psychopathological disorders documented on the first two axes can be registered. On Axis 4, possible situation-related triggers (life events) of the current mental disorder can be evaluated according to their type and stress intensity. On Axis 5, the highest degree of social adaptation in the year before the current mental disorder can be rated. This system was designed to allow a diagnosis to be made that contains as much information as possible, whereby the relevant aspects are recorded separately

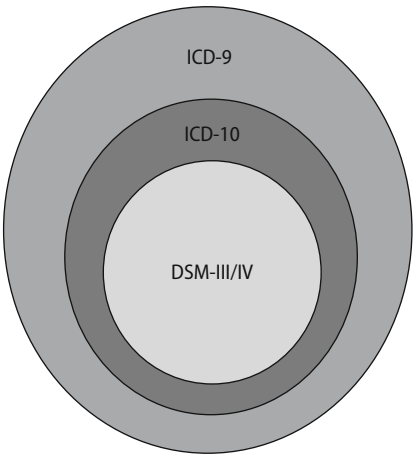

Fig. 5 The concept of schizophrenia in ICD-9, ICD-10 and DSM III/IV

in order to increase the diagnostic reliability on the one hand, and to allow recognition of new associations between the individual aspects on the other. With respect to the syndrome diagnosis on Axis 1, it is noteworthy that this does not represent at all a grammalogue for the psychopathological symptoms but that in many cases it includes hypotheses about aetiology and course. Thus, 'schizophrenic disorder', for example, can only be diagnosed on Axis 1 if an organic brain disease has been excluded. The syndrome angle was therefore obviously not consistently considered when the categories on Axis 1 were determined. Further developments of this system are DSM-III-R [8] and the now valid DSM-IV [9]. The most important advance in the DSM-III system and its successors is without doubt the considerable operationalisation of the diagnostic terms (see below).

The ICD wanted to continue this principle with its 'diagnostic guidelines' and 'research criteria', which are given in addition to the general description of a disorder, in order to improve the reliability of the clinical diagnosis. When the most recent, tenth, revision of the ICD was developed [290] an attempt was made to achieve the greatest possible compatibility with the DSM-IV.

The introduction of computers into psychiatric diagnosis meant that more complicated algorithms could be applied than possible in the simple operationalisations described above. Thus, all the information from standardised rating scales of psychopathological features, together with additional anamnestic and other information, can be processed by computer. For example, in the CATEGO program [149, 280], syndrome profiles are derived from the comprehensive rating scale PSE (Present State Examination). These are then processed in a further step, including additional information about psychopathological peculiarities in earlier phases of the illness as well as aetiological factors, to achieve a nosological diagnosis. The usability of this procedure was demonstrated in various large research projects, among others in the USA/UK Project [60] and the International Pilot Study of Schizophrenia [287] mentioned above. However, apart from the CATEGO System such time-consuming and, as far as the computer technicalities are concerned, complicated approaches are much less common today than operationalised diagnostic approaches following the algorithm of DSM-III, DSM-IV and ICD-10, which have also been computerised using relevant evaluation instruments. Over the last decade a series of fully structured evaluation and diagnosis instruments have been developed which refer to ICD-10 or DSM-III-R/DSM-IV diagnoses, or both: the composite international diagnostic interview (CIDI)[281], the structured clinical interview for DSM-III (SKID) [282] and the schedules for clinical assessment in neuropsychiatry, which is based on PSE classes (SCAN) [288].

It is not fully clear whether the categorical diagnostic entities used in DSM-III/IV or ICD-10 are conceptualised only as a syndrome or as a disease entity. As the term 'disease' is completely avoided and replaced by the term 'disorder', apparently a syndromatic approach seems to be the leading principle. The 'atheoretical' descriptive approach was underlined in several contexts, for example when terms like 'endogenous' or 'neurotic' were excluded, because they have too much causal implications. However, among other things, the differentiation between organic/exogenic disorders and non-organic/non-exogenic disorders seems to hint that the classificatory approach is not exclusively syndromatic but also takes into account knowledge about easily diagnosed causative factors. Furthermore, the chapters on schizophrenia and bipolar disorders seem to follow the traditional concepts of the so-called "endogenous" psychoses, thus representing the Kraepelinian systematic.

Some of the diagnostic constructs in the DSM-III and DSM-IV systems deviate considerably from those in the ICD-9 or ICD-10. For example, the definition of schizophrenia in DSM-IV is more restrictive than in ICD-10 or ICD-9 (Fig. 5), and less restrictive concerning the diagnosis of an affective disorder, which has prognostic implications, among others. This is also the case in comparison with some other traditional classification systems. A so-called polydiagnostic approach has been advocated in the past, especially in the 1980s [40, 133, 140, 206, 232, 233], based on the train of thought that perhaps each of these systems could be more valid under certain aspects, some of which may as yet be unknown. In such an approach, a series of different diagnostic criteria are applied simultaneously, making it possible to compare one set of study results with another in which at least one of the diagnostic systems was also applied. Furthermore, it allows various validity aspects of the respective diagnosis system to be investigated, e.g. the relationship to biological deviations and to treatment success, and the relevance for long-

term prognosis [117, 132, 191, 214]. In the long term this could result in more valid diagnostic concepts. In recent years, the increasing dominance of DSM-III-R/DSM-IV and ICD-10 has unfortunately reduced the importance of this polydiagnostic approach.

The Kraepelinien dichotomy in the view of modern follow-up research

Because most psychiatric disorders lack clear biological correlates, follow-up studies on their course, outcome and prognosis are traditionally viewed as playing an important role in psychiatric research, especially in terms of validation of psychiatric diagnoses and other psychiatric concepts, for example negative symptoms. Only a few studies have addressed the differences between the course of schizophrenia and that of other psychiatric illnesses. These studies basically come to the same conclusion that the course and outcome of schizophrenia is less favourable than that of affective and schizoaffective disorders [108, 114, 179, 186, 208, 267].

More recent research in this area has criticised this dichotomic view. A small subgroup of patients with affective disorders has recurrent episodes and does not have such favourable courses of illness as was once believed [100]. But when interpreting these results it should be remembered that the DSM-III/IV classification was used; its broad definition of affective disorders, including mood incongruent psychotic symptoms (see Chaps. 6, 7), among others, might have led to these results [62]. Furthermore, although patients with unipolar or bipolar depression do not always achieve full remission, and an outcome defined by chronic symptoms or a subsyndromal residual state is not infrequent, this cannot be compared to the personality change associated with a persistent and severe deficit syndrome, which is typical for the majority of patients with schizophrenia. Nevertheless, altogether the course of affective disorders and of bipolar disorders in particular is more polymorphic and includes more often a problematic outcome than traditionally assumed [181]. On the other hand, Bleuler [27] and many other studies [119, 120, 177] have shown that schizophrenia is not necessarily associated with poor outcome. A large subgroup of patients experiences a phasic course without developing a deficit syndrome. This heterogeneity in outcome may depend on a variety of factors, such as the severity of symptoms at onset, comorbidity, expressed emotions of relatives, social support, working conditions, stressful life events and the sociocultural environment [90].

In a 15-year, long-term, follow-up study [202], we used a comparative approach to assess course and outcome in terms of psychopathological and psychosocial aspects of 197 patients with schizophrenic, schizoaffective and affective psychoses [203]. All patients were hospitalised for the first time in the years 1980–1982 in the Munich psychiatric university hospital. Some of the main results on global, psychopathological and psychosocial outcome will be presented below.

The following typology, which has some similarities with the concept proposed by Watt et al. [274], was used to categorise global long-term outcome in a global way:

Single episode. The symptoms of the index episode disappeared completely. No further signs of a functional psychosis occurred during the study period.

Episodic-remitting course. Further episodes of a functional psychosis occurred during the study. The GAS score was not consistently lower than 61 in the two years before the follow-up study.

Chronic course. During the course of the disorder there was never a complete remission of symptoms and/or further episodes of a functional psychosis occurred. The GAS score was consistently lower than 61 in the two years before the follow-up study.

This is a rather rough classification of typology, although it is comprehensible from a clinical, pragmatic viewpoint. The chronic course type was operationalised with the help of the global assessment scale (GAS) score, similar to Harrison et al. [113]. The Vermont longitudinal study differentiated between a favourable and unfavourable course in a similar way [112]. Möller et al. [205] were able to show that the GAS score is a suitable global outcome parameter that correlates closely with other outcome dimensions [125].

All available sources of information (interviews with the patient, his relatives and treating physician, medical records) were included in the classification of the course type. 57% of patients with a diagnosis of schizophrenia were found to have a chronic course (Fig. 2), but only 3% of patients with affective disorders and 15% of patients with a schizoaffective psychosis.

Outcome description in terms of negative symptoms is of special interest. The presence of negative symptoms in schizophrenia was described early on by Kraepelin [150] and Bleuler [25, 37]. In Kraepelin's dichotomic concept of schizophrenic versus affective psychoses, negative symptoms, conceptualised as the deficit syndrome, were fundamental. Kraepelin considered schizophrenia to be a non-remitting illness characterised by continuous deterioration with predominating negative symptoms.

The analysis of the psychopathology scales of the Munich 15-year follow-up study found that patients with a diagnosis of schizophrenia had significantly more negative symptoms after 15 years. This became especially clear when results were analysed according to the concept of a deficit syndrome [55], which describes chronic negative symptoms persisting for at

least 1 year that cannot be explained as being secondary effects of extrapyramidal or depressive symptoms or of social deprivation [36, 37, 202, 203]. The relevance of negative symptoms was also described in other follow-up studies, also with respect to outcome prognosis [200, 204, 208, 284].

The main features of Kraepelin's concept are confirmed by the results from recent studies of disease course, which show the unfavourable course of schizophrenic psychoses and the frequency and relevance for differential diagnosis of negative/deficit symptoms. Schizophrenic psychosis has been shown to have a more unfavourable course than affective psychosis [177].

The question remains whether great importance should be placed on aspects of course for the differentiation of different groups of non-organic psychoses or whether other parameters, e.g. neurobiological, are more suitable to define valid and, with respect to biological factors, meaningful diagnostic entities. In his commentary on long-term studies, Kendell [141] wrote: 'Despite its many imperfections, the concept of schizophrenia is unlikely to be abandoned until we have radical new insights into the etiology of the "functional psychosis" [57]. Is the familial cosegregation of schizophrenia and bipolar disorders [52] such a radical new insight that it justifies abandoning the concept of schizophrenia and the Kraepelinian dichotomy?'

If the aim is to define disease symptoms on the basis of neurobiological parameters, neurobiology, particularly in the context of follow-up studies, should not only be understood in the sense of neurogenetics and molecular biology but should also include neuropathological findings [31, 32, 122, 152, 275, 276] or their *in vivo* surrogate, MRI, together with results from neurophysiological evaluations, etc [93, 115, 222, 249, 251]. For example, the results of structural MRI research show not only that patients with schizophrenic disorders have marked alterations in brain structure, e.g. ventricular enlargements and hippocampus atrophy, even in the premorbid stage - which can be interpreted as corresponding with the neurodevelopmental hypothesis [237, 247–249]—but also that further brain alterations can occur during the course of the disorder [45–47, 159, 161, 187]. These structural brain changes are interpreted as being the result of progressive neurobiological processes of unexplained cause, which may be associated with immunological processes [223] or changes in the glutamatergic system or other parameters. Although such alterations of brain structure are also found in patients with affective disorders, they are not so pronounced and evidently not or only to a minor degree progressive [95, 96]. Both in terms of neurodevelopment aspects [225] as well as in terms of a neuroprogressive process schizophrenia might be dissimilar to affective disorders.

Of course, the neurotransmitter systems and the related molecular genetics still have a place in future research, especially in the concept of the classical dopamine hypothesis of schizophrenia, although the glutamate and the serotonin system are also of special interest [1, 18, 34, 53, 104, 109, 121, 154, 160, 243, 245, 252, 265].

The challenge to the Kraepelin dichotomy: the overlap between symptoms of schizophrenia and affective psychoses as a classificatory dilemma

The traditional hierarchical approach to psychiatric classification in the sense of Jasper's layers-rule ('Schichtenregel') gave more weight to those symptoms which he interpreted as being the most relevant in the diagnostic hierarchy, e.g. a patient who suffered from schizophrenic and depressive symptoms was diagnosed as having schizophrenia. One of the implications of this principle was that, in most cases, a patient was given only one diagnosis. The development of the operationalised diagnostic systems ICD-10 and DSM III/IV changed this strategy. Nowadays, a patient can be diagnosed as having several disorders simultaneously, if the relevant symptom- and time-related criteria for the particular clinical diagnoses are fulfilled. Comorbidity has thus become a central issue of current psychiatric classification [236]. If the criteria for a certain disorder are not completely fulfilled, a subthreshold comorbidity can be considered. The epidemiological studies performed during the development of the DSM and ICD-10 systems paid great attention to the principal of comorbidity and proved empirically that if this approach is followed, there is a high degree of full or subthreshold comorbidity with other psychiatric disorders in almost all psychiatric disorders, including schizophrenic psychoses.

Although the concept of comorbidity seems principally meaningful if it describes the coexistence of two clearly separated entities, for example schizophrenia and alcohol addiction, this approach leads to an inflation of diagnoses when it comes to disorders with a rich picture of different symptoms, as is the case with schizophrenia. The modern diagnostic systems describe the simultaneous existence of several syndromes as comorbidity, although it could actually be better described as cosyndromality, given the fact that these syndromes are apparently not independent of each other but often covariate over time. This kind of comorbidity was criticised for disrupting the coherence of the complex phenomenology of these disorders and for inducing the idea that each of this comorbid disorders might have to be treated with a different drug [169].

As mentioned above, schizophrenia is not only characterised by a paranoid-hallucinatory syndrome but also by a negative syndrome. Schizophrenia is

therefore a cosyndromatic condition per se and its clinical picture is also enriched by other syndromes not belonging to the core/pathognomonic symptoms, e.g. depressive symptoms. If a comprehensive rating scale like the association for methodology and documentation in psychiatry (AMDP) system [19, 28–30, 44, 97, 235, 253] is applied, which covers more or less all relevant symptoms of the psychopathological spectrum of schizophrenic and affective psychoses (Fig. 1), the complex psychopathological pattern of schizophrenic patients in terms of cosyndromatic conditions becomes obvious. The similarities and dissimilarities of the syndrome profiles also become evident when schizophrenic patients are compared with schizoaffective and affective patients, who are also often characterised by several syndromes. The change in the mixture of the cosyndromatic conditions can be demonstrated in follow-up studies with cross-sectional ratings at certain time points (Fig. 1).

It is a question of diagnostic tradition or current diagnostic consensus, and therefore to a large degree arbitrary, whether the coexistence of several psychopathological syndromes is conceptualised as cosyndromatology or comorbidity. The same is true for the criteria related to symptom intensity or configuration of symptoms, which are used in this context to describe the time after which a cosyndromality becomes a comorbidity. Apparently, DSM III/IV and ICD 10 apply different strategies in dealing with this in the context of different disorders. For example, other principal rules appear to be applied for the differentiation of schizophrenia and depression than for differentiation of depression and anxiety, which leads to principal differences in the possible amount of comorbidity.

In addition to cross-sectional depressive cosyndromality/comorbidity, which has been referred to above, there is also a longitudinal comorbidity, i.e. lifetime cosyndromality/comorbidity. In the sense of the traditional theoretical concepts of schizophrenia, depressive symptoms occurring before the appearance of positive symptoms would be seen as prodromal symptoms of schizophrenia, when occurring simultaneously as depressive symptoms accompanying the positive symptoms of the acute schizophrenic episode, and when apparent afterwards as a post-psychotic depression occurring after the positive symptoms have abated. With the comorbidity approach these depressive symptoms can apparently become independent ‘disorders’/‘illnesses’, as long as the relevant ICD-10 and DSM-IV criteria are fulfilled. On the one side this has the advantage that certain subtypes or special forms of the illness can be more easily defined and investigated. On the other side, for everyday clinical practice this conceptualization has the disadvantage that the concept of schizophrenia, which was assumed to be homogeneous, is broken up into many sub-aspects and the inner relationship of the distinct syndromes becomes harder to understand. Although this is also true for cross-sectional comorbidity, it becomes even more obvious in the example of life-time comorbidity [183].

Of great interest in this context are the data collected by Häfner et al. [111] in the context of their so-called ABC schizophrenia study and ABC follow-up schizophrenia study. As the psychosis remitted, the proportion of patients presenting depressive symptoms decreased and on average remained stable in the further course. Its frequency at the prodromal stage and in relapse episodes of schizophrenia suggests that depression might at least to some degree be considered an early, milder stage of the same neurobiological process that finally leads to psychosis. Häfner et al. concluded from these data that the high prevalence of depression in the general population is triggered by various psychological or biological factors and its occurrence at the prodromal stage of numerous brain diseases suggests that depression might be a mild, genetically determined reaction pattern of the human brain. As the underlying brain dysfunction increases, more severe reactions patterns, e.g. psychosis, are produced. In the authors’ opinion, an implication of this assumption would be to return to a hierarchical model of psychopathology dimensions as proposed by K. Jaspers in 1913 and E. Kraepelin in 1920.

The following part will focus on the coexistence of psychotic (schizophrenic) symptoms and depressive/manic symptoms to discuss a principle diagnostic dilemma: can the coexistence of these symptoms be seen as an integral part of schizophrenia or affective disorders? Is this a comorbid condition? Is this related to a special disorder like schizoaffective psychoses? Is the differentiation between mood congruent and mood incongruent psychotic symptoms of relevance in this context (Fig. 7)?

While coexisting or even sequentially appearing depressive, anxious or compulsive symptoms were traditionally seen as a symptomatological part of the complex psychopathological phenomenology of schizophrenic psychoses, and no additional conclusions were usually drawn, particularly not with respect to aetiopathogenetics, the modern idea of comobidity appears to express more, i.e. it means not only coexisting symptoms or syndromes, but apparently the coexistence of two illness entities (morbus = illness). However, such a development of this idea is difficult to understand based on the overall conceptualization of the ICD-10 and DSM III/IV systems since these claim to use a descriptive, syndrome-oriented approach, at least for the functional/nonorganic disorders, without assuming a ‘morbus’ (illness with special course and special aetiopathogenesis). Thus, one refers to ‘major depression’ or a ‘depressive episode’, for example, and the associated classification criteria are mainly symptomalogical/syndromatological while temporal criteria are secondary.

Aetiopathogenetic hypotheses should not play any part in the formation of a diagnosis, apart from the exclusion criterion that there should be no aetiopathogenetically plausible relationship with an organic causation. A 'morbus' concept is generally not assumed in the ICD-10 or DSM III/IV description of schizophrenia or affective psychoses, part of which would be a positive association with aetiopathogenetic factors, e.g. familial clustering of a disorder in the sense of a genetic predisposition [264]. Based on this argumentation the term 'cosyndromatology' seems to be more appropriate than the term 'comorbidity'.

Thus, the ICD-10 and DSM III/IV systems mostly define syndromes of non-organic disorders, which are then determined as a diagnostic entity in the sense of a 'disorder' using somewhat arbitrary criteria with respect to number, severity and time course of symptoms. Epidemiological investigations, which are based solely on these criteria and do not include any other aspects, such as hypothetical organic aetiopathology, for example, would therefore actually only be able to define cosyndromalities and not comorbidities in the stricter sense. This differentiation may appear to be hairsplitting or even irrelevant, but on closer inspection it is not. A real comorbidity approach in the sense of comorbidity of schizophrenia and depression would mean, for example, that not only are symptoms of an affective disorder present (which may correspond to a certain list of diagnostic criteria) in addition to those of a schizophrenic disorder, but that at least hypothetically besides aetiopathogenetic factors for schizophrenia there are also some symptoms for any affective disorder, e.g. a relevant hereditary trait for affective disorders.

The results from respective epidemiological investigations in the general population and studies of in- and outpatients show high rates of comorbidity [69, 80, 81, 103]. This is not surprising since, even in times before the introduction of operationalised diagnostic criteria, comorbid symptoms from these psychopathological areas were repeatedly noted, in particular the frequency and clinical relevance of depressive symptoms [153, 271].

ICD-10 addresses the coexistence of schizophrenia and depression in two categories: the postschizophrenic depression (PSD) and the schizoaffective disorder, depressive type. Of course, this is only a limited approach because, as mentioned above, there are other depressive conditions in schizophrenia than just post-schizophrenic depression and schizodepressive disorder. The diagnostic criteria of the DSM-IV for depression in schizophrenia are still among the Criteria Sets and Axes Provided for Further Study, called postpsychotic depressive disorder of schizophrenia (PDDS). Both criteria sets for postpsychotic depression are based on the criteria for depressive episodes with some modifications, and include an item to avoid the diagnosis of a depressive episode during the acute psychotic episode. The DSM-IV criteria include an item to exclude depressive symptoms that are better accounted for as medication side effects or negative symptoms. The main incompatibility between the criteria is the fact that the ICD-10 PSD criteria limit the diagnosis of depressive episode to the 12 months following the psychotic episode, while the DSM-IV PDDS criteria do not have time limitations [39]. Apparently the concept of PDS in ICD-10 tends to avoid a comorbidity in the stricter sense. This becomes especially obvious in the last sentences of the guideline formulation (see Table 1), which underline that in the case of mixed conditions either the diagnosis of a depressive episode or of a schizophrenic episode should be given, depending on the prominent feature.

Cross-sectional comorbidity in the sense of ICD-10/DSM-IV could be defined if a patient fulfils the full criteria for two disorders at the same time, e.g. a comorbidity of a depressive episode and a schizophrenic episode separate from a schizoaffective disorder. Of course, these strict criteria could be weakened to cover those conditions where there is a coexistence of the symptoms of two disorders, without reaching the full criteria (subsyndromal comorbidity). Similarly, lifetime comorbidity could be defined longitudinally for the sequence of different disorders.

There is no category to describe the coexistence of schizophrenia with manic symptoms apart from the category 'schizoaffective psychosis'. Schizoaffective psychosis is a special model example of the close interlocking of two disorder groups. It was traditionally not only conceptualised as a cosyndrome or comorbidity but as the result of an aetiopathogenetic amalgamation process between schizophrenic and affective disorders, which may be supported at least partially by family-genetic and also other aetiopathogenetic findings. The mere description in terms of cosyndromality or comorbidity would not reach the full content of this concept. The repeatedly discussed unitary psychosis ('Einheitspsychose'), which fully combines the schizophrenic and affective psychosis as belonging to the same continuum of psychosis [77] with a common aetiopathogenetic background, can be seen as the extreme of this conceptualization [92, 153, 167, 174, 175, 271].

Angst [11] performed a very comprehensive review of the historical aspects of the dichotomy between schizophrenia and affective disorders. He stated that Guislain [110] and Zeller [292] established a unitarian concept of psychiatric disorder, permutations of which have survived until the present day. Kraepelin's dichotomy [148] between 'manic-depressive insanity' and dementia praecox was built mainly on Kahlbaum's classification [129], which took clinical symptoms, course and outcome into account. Kraepelin's well-accepted approach sought to provide a basis for diagnosis, prognosis, choice of treatment and causal research. Kraepelin's dichotomy came to

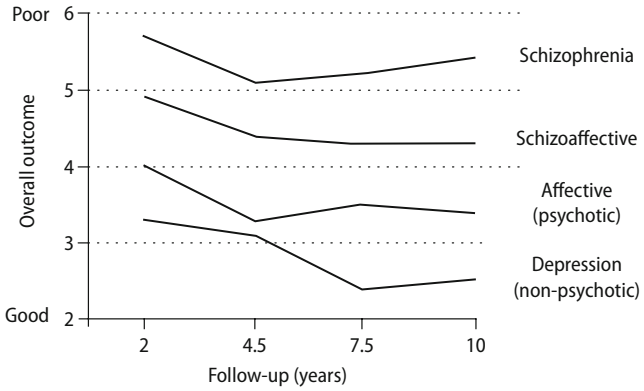

Fig. 6 Outcome for schizoaffective disorder, schizophrenia and affective disorder groups (Levenstein–Klein–Pollack scale) at four consecutive follow-ups [114]

be questioned on several grounds: (1) doubts about his unification of bipolar disorder [88] with melancholia, (2) doubts about the significance of Kraepelin's diagnostic groups for causal research [118], illustrated best by the work of Bonhoeffer [33], (3) the complex psychopathological descriptions and classifications of numerous subgroups of psychoses by Kleist [146] and Leonhard [156], and (4) description of the psychoses between affective and schizophrenic disorders (intermediate psychoses, mixed psychoses, schizo-affective psychoses) beginning with Kehrer and Kretschmer [137] and persisting up to the modern findings of a continuum between the two major groups of psychiatric disorders. In the view of Angst, Kraepelin's simplification has so far been more successful than the Kleist–Leonhard approach, but the modern and more descriptive trend in psychiatric classification favours apparently the syndromal concept already suggested by Hoche at the beginning of the twentieth century [118] and the concepts of continua between affective and schizophrenic disorders and between normal and pathological behaviour [11]. There is no doubt that, traditionally, schizoaffective disorder is seen as a syndromatological amalgamation of two disorders, not as a comorbidity of two distinct disorders/diagnostic entities. Craddock even suggest a hypothetical genetic model to explain [66].

Beside the historical development of the concept, the current conceptualization by the ICD-10 and DSM IV criteria [171, 172] represent a special type of the relevant modern conceptualization of a relationship between schizophrenic and affective symptoms. The affective part occurs either simultaneously with the schizophrenic symptoms or sequentially (without concurrent schizophrenic symptoms), depending on the diagnosis system applied [170]. There is no referral to comorbidity with an affective disorder but the conceptualization of a schizoaffective psychosis covers the whole range of phenomena with the term 'schizoaffective psychosis' itself. The earlier the prototype of a coexistence with bipolar affective symptoms becomes apparent, the more justified the concept appears. If the depressive symptoms simply coexist with the schizophrenic symptoms, or even only occur during the course of the illness without concurrent schizophrenic symptoms, the less convincing the definition of a schizoaffective psychosis appears. The less restrictive the related definition criteria are, the more diluted the concept becomes so that in the end any kind of depressive cosyndromality-/simultaneous or sequential—can correspond to the diagnostic concept of a schizoaffective psychosis. It is therefore of relevance that DSM-III/IV defines a much more restrictive concept of schizoaffective psychoses than ICD-10.

In the differentiation between schizophrenia with depressive/manic symptoms, depression or mania with psychotic symptoms and schizoaffective disorders, the psychopathological differentiation between mood-congruent and mood incongruent psychotic symptoms has traditionally played an eminent role (see Fig. 6). Mood-incongruent psychotic symptoms were assumed by classical psychopathologists—such as Karl Jaspers or Kurt Schneider—to be 'pathognomonic' for schizophrenia (if an organic or medical condition is excluded), especially the so-called 'first rank symptoms'. The DSM-IV, however, has involved mood-incongruent psychotic symptoms in mood disorders as well. But if mood-incongruent symptoms are seen to belong to mood disorders as well, there is an increased risk of confusing diagnostic entities such as 'pure' mood disorders with schizoaffective disorders and to some extent with schizophrenia and schizophrenia disorders as well. It is still necessary to find out the discriminating power of mood-incongruent symptoms, and the boundaries between pure mood disorders and other psychotic disorders (Table 3; [2–5, 175]). In this context the Chicago 10-year follow up study is of enormous importance [114]. This study compared 210 patients with schizoaffective disorder, schizophrenia, bipolar disorder and depression. Patients with schizophrenia had the poorest outcome at the follow-up evaluations compared to the other groups, especially to patients with affective disorders, while patients with schizoaffective disorders were in between (Figs. 6, 7).

The Chicago 10-year follow-up study [114] also showed impressively that the differentiation between patients who in the acute phase had an affective disorder and either mood congruent or mood incongruent psychotic symptoms is of great prognostic value since those with mood incongruent psychotic symptoms have a much poorer overall outcome (Fig. 6). This was confirmed quite consistently by other recent studies (Table 3; [59, 82, 135, 262]).

Table 3 Prognostic relevance of mood-incongruent psychotic symptoms

– Poor prognosis	Conus et al. [59], Dunayevich and Keck [82], Harrow et al. [114], Strakowski et al. [262]
– No difference	Keck et al. [135]—outpatient study!

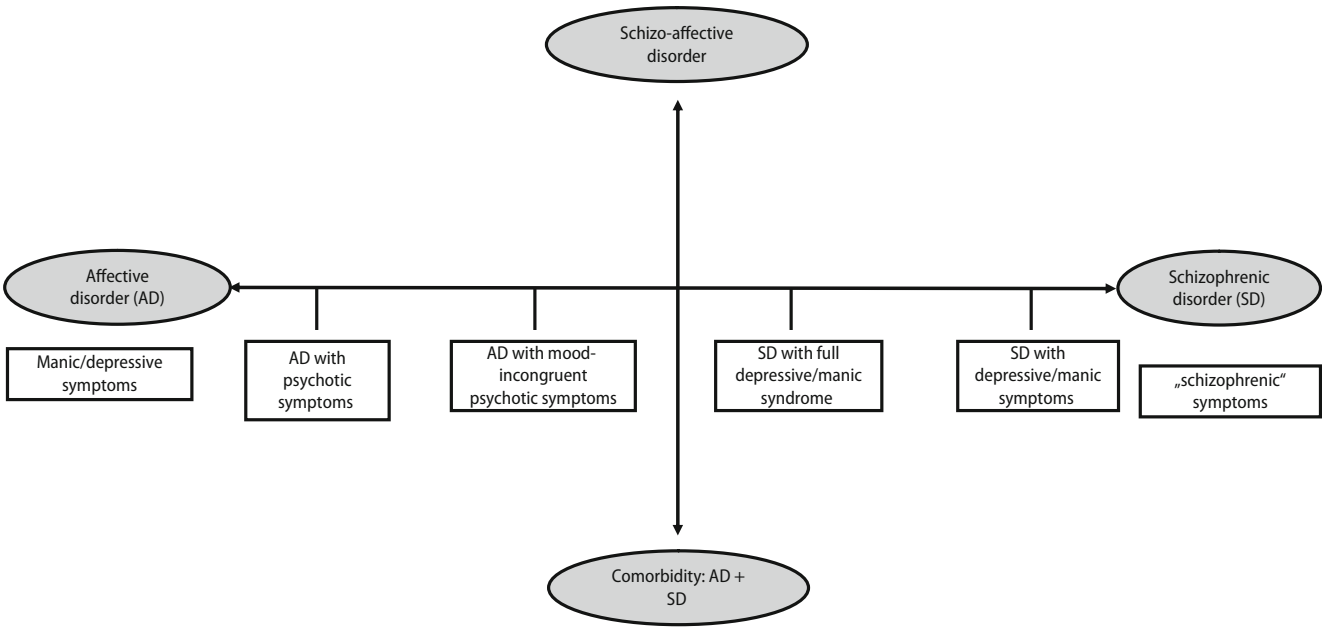

Fig. 7 The dilemma: The extended transition between affective and schizophrenia disorders [114]

Without differentiating between mood-incongruent and mood-congruent psychotic symptoms, Coryell et al. [62] found that manic patients with psychotic features in the acute index phase had a much higher morbidity burden (time with depressive or manic symptoms) than the non-psychotic patients.

Altogether these findings indicate that especially mood-incongruent psychotic symptoms can be seen as an indicator of a poorer prognosis, a fact that should be better considered in modern classification systems and that especially questions the negative approach in DSM-IV. In his recent paper Marneros [182] came to the conclusion that the special characteristics of bipolar disorder with mood-incongruent psychotic symptoms can lead to similar conclusions as polymorphism. With the term 'polymorphism' he describes the phenomenon according to which episodes other than mood episodes can also occur during the long-term course of bipolar I disorders, e.g. schizophreniform and "schizoaffective" episodes (defined as concurrently fulfilling the criteria of both schizophreniform and mood episodes). It could theoretically be possible to argue that bipolar disorders with mood-incongruent psychotic symptoms have at least two comorbid disorders: schizophrenia and bipolar disorder. Marneros [182] pointed out that the construct of comorbidity cannot explain the fact that patients with mood incongruent psychotic symptoms (like bipolar patients with a polymorphic course) differ from patients with prototypic diseases, i.e. schizophrenia or mood bipolar disorders without mood incongruent psychotic symptoms, on various relevant levels (age at onset, family history, outcome etc.). He suggested that perhaps the answer can be found in the 'antagonistic influence' of both genetically determined or co-determined disorders, the result of which is a position of mood disorders with mood incongruent psychotic symptoms in-between the two prototypes.

The future development of the systematic of psychiatric disorders

Preparatory work for DSM V and ICD-11 has commenced in the last few years [127, 238]. Both systems will potentially change the traditional classification of psychiatric disorders to a much greater degree than was the case with DSM IV and ICD-10. For example, they will potentially omit the dichotomy between schizophrenic disorders and affective disorders. It cannot be ruled out that in the end a broad category 'psychotic disorders' may be developed, which can be subdefined by a dimensional/syndromal approach. The DSM-V Prelude Project considers the following issues as the starting point for the development of a new systematics of psychiatric disorders [91]:

- Despite many proposed candidates, not one laboratory marker has been found to be specific in identifying any of the DSM-defined syndromes.
- Epidemiological and clinical studies have shown extremely high rates of comorbidities among the disorders, undermining the hypothesis that the DSM syndromes represent distinct aetiologies.
- The efficacy of many psychotropic medications cuts across the DSM-defined categories. This relates, for example, to SSRIs being equally effective for 'depression' and 'anxiety disorders', even though they are different DSM entities.

- Reification of DSM-IV entities to the point that they are considered equivalent to diseases is more likely to obscure than to elucidate research findings.
- It can be concluded that the field of psychiatry has thus far failed to identify a single neurobiological phenotypic marker or gene that is useful in making a diagnosis of a major psychiatric disorder or for predicting response to psychopharmacologic treatment.

Currently, only some ideas about the future development of the systematics of psychoses can be derived from the recent internet publication of the fifth planning session in February 2006 of the DSM-V prelude project 'deconstruction of psychosis' [91]. The title of this project seems to underline the potential progressiveness of this approach. At the conclusion of the presentations the participants formed two breakout groups to discuss the presentations in greater detail and to formulate recommendations (report from 91). Because the participants included not only US-American experts but also experts from other countries, who tried to harmonise right from the start between DSM-V and ICD-11, the recommendations seem to reflect a more general international view on the dichotomy of schizophrenic and affective psychoses. Altogether, the recommendation indicates a high degree of discrepancy concerning both the validity problems of the dichotomy as well as possible solutions. The recommendations from the first group included:

- Replacing the current categories with a general psychosis syndrome that would cover a broad range of disorders ranging from schizophrenia, schizoaffective, delusional and brief psychotic disorders, to bipolar disorder and psychotic depression.
- Reducing the duration criterion for schizophrenia from 6 months to 1 month.
- Including dimensionally specified criteria in the research appendix for positive symptoms, negative symptoms, depression, mania, cognitive decline, and functional impairment.
- Including research specifiers for duration, time course, and mode of onset.

The second group recommended:

- Harmonizing the discrepancy in the schizophrenia duration criteria between DSMssssss and ICD by conducting reanalysis of prospective studies that have data points at periodic (e.g. monthly) intervals up to 12 months, with the aim of ascertaining which duration cut point maximises chosen validators (e.g. diagnostic stability, outcome, social adjustment).
- While agreeing that the schizophrenia/bipolar dichotomy has some validity problems, group members expressed reservations about the impact on clinical utility of abandoning this distinction.
- Since a large proportion of individuals fall into the overlap area between schizophrenia and bipolar disorder and are currently diagnosed as schizoaffective, or 'Psychotic/Mood not otherwise specified', studies are needed to focus on these problematic cases with respect to treatment response, laboratory studies, prognosis and outcome.
- Another approach might be to parse out homogeneous subcategories of schizophrenia and bipolar disorder with respect to aetiology, treatment response, outcome; e.g. deficit syndrome.
- If the categorical approach is retained in DSM-V, there is a pressing need to improve definition of schizoaffective disorder.
- The group agreed that ultimately there will be need for an dimensional approach to psychosis/mood disorders and suggested that research be carried out to determine which dimensions to use and how they should be measured.

Craddock and Owen recently published a paper [68] with the critical title: 'Rethinking psychosis: the disadvantages of a dichotomous classification now outweigh the advantages'. This paper, published in the WPA journal *World Psychiatry*, was published in a forum with the provocative title: "Do the disadvantages of the Kraepelinian dichotomy now outweigh the advantages?" Several international experts, such as Carpenter, Murray, Angst, Brockington, Marneros and others, commented in this forum on the paper by Craddock and Owen. Craddock and Owen, who were the most active critics of the categorical classification and the Kraepelin dichotomy, have written several other similar papers, for example 'The beginning and the end of the Kraepelinian dichotomy' [67] or 'Do current classifications inhibit processes in research and clinical practice?' [68]. Their argumentation is based predominantly on genetic aspects [66, 68] without considering the many other aspects of the systematics of psychiatric disorders. Their main point is the genetic overlap between schizophrenia and bipolar disorder but they omit to consider that there is also inconsistency in the overlap when it comes to syndromes or even symptoms and their possible genetic association [61, 105]. They give no clear direction as to how the psychiatric classification should be changed, apart from general recommendations that either nosological categories better fitting the neurobiological findings (of course, in their view, primarily genetic findings) or a syndromatological systematics should be established.

The following points are part of the central part of their argumentation:

Evidence from genetic epidemiology has been gradually accumulating over the past two decades that is inconsistent with the dichotomous view, and recent molecular genetic findings seem set finally to overturn it. Key pieces of evidence include the following:

– Family studies point to the existence of a non-trivial degree of familial coaggregation between schizophre-

nia and bipolar illness and between schizoaffective disorders and both bipolar disorder and schizophrenia (reviewed by [65]).
- A recent twin study—the only one that has used an analysis unconstrained by the diagnostic hierarchy inherent in current classification systems—demonstrated an overlap in the genetic susceptibility to mania and schizophrenia [52] and provided evidence that there are genes that confer susceptibility across the Kraepelinian divide to schizoaffective disorder and to some cases of schizophrenia and bipolar disorder. This study also confirmed the traditional notion that there are genes specific to the two prototypical disorders.
- Systematic, whole-genome linkage studies of schizophrenia and bipolar disorder have implicated some chromosomal regions in common; this is consistent with the presence of shared susceptibility genes [24, 65].
- Most recently, and most convincingly, genes have been identified in which variation appears to confer risk to both schizophrenia and bipolar disorder [65]. One example is the gene-encoding D-amino acid oxidase activator (formerly known as the G72/G30 locus) on chromosome 13q. Another example is the gene Disrupted in Schizophrenia 1 (DISC1).

The arguments based on genetic findings cannot be ignored. However, the magnitude of relative risk mediated by sequence variants in each specific susceptibility gene is very modest [143] (see the paper of W. Maier in this issue), and some experts claim that altogether the percentage of explained variance is lower than 10%. Therefore, it seems to be premature to base a new classification of psychoses on these findings [224, 251]. From a neurodevelopment point of view, including both schizophrenic and manic-depressive disorders, it is also not too surprising that disorders that are part of human growth and maturation have several genes in common, and that epigenetic factors play an important additional role [251]. From a clinical point of view it can be questioned why the arguments focus primarily on a spectrum of schizophrenic and bipolar disorders while unipolar depression, which was included in Crow's continuum concept [73], with its special feature of a psychotic depression, is not included. Thus, the psychotic continuum seems incomplete.

In the same issue of *World psychiatry*, Carpenter [56] comments on the paper and suggestions made by Craddock and Owen from a more psychopathological view. He comes to the conclusion that DSM V and ICD-11 will have to retain the major diagnostic classes because there is not enough knowledge to radically revise the nosology for these illnesses. He suggests addressing the shortcomings of the current classification system by developing a parallel system based on domains of pathology like the dimension of negative symptoms, disorganization, reality distortion, cognition etc. His argumentation is a good example for a more clinical approach to the question of how to classify/describe psychoses. "Schizophrenia is a clinical syndrome. It has not been documented as a single disease entity. Nonetheless, most study designs during the twentieth century investigated schizophrenia as a class. This may be analogous to studying dementia rather than specific entities such as Alzheimer's disease. Since specific disease entities had not been identified within the schizophrenia syndrome, we proposed using domains of pathology to reduce syndrome heterogeneity. This was based on the tripartite model that we published in 1974 [263], viewing schizophrenia as comprising positive psychosis, negative symptoms, and impairments observed in interpersonal relations. These domains were found to be rather independent of each other in our studies. Implementation of this model would be a paradigm shift, as we advocated the study of each pathologic domain as the independent variable allowing for differences in etiology, pathophysiology, and treatment between pathologic domains within the syndrome boundaries. However, at that time, the concept of nuclear schizophrenia was dominant and only recently has the domains of pathology paradigm received wide attention. The 1982 type I/II [70] and positive vs. negative [10] proposals attempted to move the domains paradigm forward, but the dominant paradigm held sway. Cognition impairment and negative symptoms are now the focus for drug discovery, with the assumption of relative independence between these pathologies and psychosis [42, 145]" [56].

In his comment on the article by Craddock and Owen, Murray [224] warns against being too radical and suggests that the traditional categorical system should be combined with a dimensional approach. This combined approach should be further validated with neuroimaging, neuropsychology, molecular genetics etc. He argues that the effect of individual genes on susceptibility to different psychiatric disorders is likely to be too small to be useful in drawing up a novel classificatory system. Furthermore, while it is certainly true that evidence against the validity of the Kraepelinian dichotomy is mounting, he underlines that it is premature to argue the case using molecular genetic data because of their inconsistency, which he then refers to: different methods of meta-analysing whole-genome linkage scans of bipolar disorder and schizophrenia have yielded different results. For example, using the technique of multiple scan probability, Badner and Gershon [20] found common loci for both disorders on chromosome 22q, as well as two distinct susceptibility loci. On the other hand, Craddock and Owen were co-authors of a rank-based meta-analysis of schizophrenia and bipolar disorder, which showed significant evidence for linkage to several chromosome regions in schizophrenia [158], whereas no region achieved genome-wide statistical significance in bipolar disorder [258].

Maziade et al. [184] undertook a genome scan of schizophrenia and bipolar disorder in multigenerational families affected by schizophrenia, bipolar disorder or both. Their work was based on the hypothesis that susceptibility genes may be shared by the two major psychoses (the common locus phenotype). Their results showed convergence in some regions, but suggested that other susceptibility genes may be specific to each disorder.

"Our group's previous twin study also supports the idea that schizophrenia and bipolar disorder may share some common genes, while others may be specific to each condition [52]. We have used these data to argue elsewhere that developmental and dimensional perspectives are likely to throw the greatest light on the relationship between schizophrenia and bipolar disorder [83, 225]. Thus, neuropsychological and grey matter deficits are much more noticeable in schizophrenia than bipolar disorder [185, 239], as are neurological soft signs. Indeed, children who later develop bipolar disorder do not share the excess of subtle neuromotor and cognitive impairments of their pre-schizophrenic counterparts and often appear superior to the normal population in motor development and school examinations [49]. Furthermore, the risk-increasing effect of obstetric complications appears to be confined to schizophrenia [50]. Exposure to perinatal hypoxia is known to result in smaller volume of the amygdala and hippocampus, which are reduced in schizophrenia but not in bipolar disorder. These findings suggest that one distinction between schizophrenia and bipolar disorder is that there exists a gradient of neurodevelopmental impairment which is much more important in the former than the latter" [224].

Angst's [13] comment to Craddock and Owen focuses primarily on studies performed in the first decades after Kraepelin, describing some aspects of invalidity of the dichotomy, especially the phenomena of a intermediate group between schizophrenic and affective psychoses named atypical psychoses, mixed schizoaffective psychoses, etc. He states that Kraepelin himself wrote in a publication in 1920 [151] that it is quite frequent that a clear clinical decision between dementia praecox and manic depressive insanity is not always possible. Like the great antagonists of Kraepelin, Hoche [118] and Bumke [43], who preferred a purely descriptive syndromal approach and assumed that identical syndromes can have multiple causes, Angst recommends a careful and unselected description of symptoms as the most important factor for the future development of classification of psychiatric disorders.

Marneros' [173] is of a similar opinion and points out that in his concept of 'dementia praecox' and 'manic-depressive insanity' Kraepelin described 'prototypes' rather than straight entities having impermeable boarders.

In the general discussion about future diagnostic systems in psychiatry, cognitive disturbances were suggested as an important subdimension of schizophrenia that should become more important. Keefe recently published a comprehensive and balanced review [136] of the findings on cognitive disturbances in schizophrenia. These disturbances are prevalent years before the psychotic breakdown, are only partially associated with acute psychotic symptoms, are more or less stable or can even increase over the longitudinal course of schizophrenia, in cross-sectional assessments are closely associated with social functioning and also predictive for long-term outcome in terms of social functioning, and are more pronounced in patients diagnosed with schizophrenia than in those with (non-psychotic) affective disorders. Cognitive dysfunction reaches a highly relevant level in the majority of patients, including those with chronic schizophrenia, and not only first-episode patients have a cognitive performance one standard deviation below that of healthy controls. All these are good reasons for Keefe to suggest that cognitive impairment should be included in the diagnostic criteria for schizophrenia, either in a categorical or syndromatic way.

Such an inclusion of cognitive disturbances would correspond very well with the traditional concept of dementia praecox/schizophrenia as suggested by Kraepelin and Bleuler [201], both of whom considered cognitive disturbances to be of great importance, beside negative and positive symptoms. Kraepelin's term 'dementia praecox' underlines this precisely, although apparently he had not only the cognitive deterioration in mind but also the change of personality in terms of negative symptoms. Similarly, Bleuler's concept views cognitive alterations and negative symptoms as core symptoms of schizophrenia, while the positive symptoms in the sense of our modern nomenclature were seen to be accessory symptoms [192]. The predominance of positive symptoms in the concept of schizophrenia was established later on, especially with Schneider's concept of first-rank symptoms which, to quote Schneider, appear to be the most reliable criteria to diagnose schizophrenia. Although it became apparent that first-rank symptoms are not sufficient to diagnose schizophrenia, and that they can also be part of other non-organic (and, of course, organic) psychoses, the focus on positive symptoms in the diagnosis of schizophrenia was adopted by our modern diagnostic systems DSM-IV and ICD-10. These diagnostic systems did not give much consideration to negative symptoms and particularly not to cognitive disturbances. In the context of the neurodevelopmental theory, cognitive disturbances were interpreted as being a vulnerability marker indicative of subtle brain alterations, and modern neurogenetics apply cognitive impairment as an endophenotype for genetic research [38, 101, 116, 144, 189, 237, 244, 246, 277]. The interest in cognitive symptoms of schizophrenia was especially renewed with the introduction of the second generation

antipsychotics, which are believed to have a somewhat stronger impact than the first generation antipsychotics on both negative symptoms and cognitive disturbances [193, 286]. As to future drug development, there are tendencies to focus much more than before on these dimensions of schizophrenia, which could result in the development of drugs mainly targeted at cognitive disturbances in schizophrenia. Thus, the idea of a drug therapy specifically tailored to targeting different domains of schizophrenia was born a long time ago, although this idea has not yet been realised in the sense of a licensed drug. As mentioned by Keefe, modern epidemiological and follow-up research describes very clearly that cognitive impairment is a core symptom dimension of schizophrenia.

In the old days the group of cognitive deficits consisted primarily of those disturbances which can be observed directly during psychiatric exploration without specialised neuropsychological testing, e.g. attention deficits, deficits in abstract thinking, thought blocking, incoherence, etc. These symptoms are still included in some schizophrenia rating scales, like the PANSS. Huber coined the term (cognitive) basic symptoms [107] for the subjective experience of these cognitive deficits on a level which is not accessible by the observer but only by the patient himself. This concept of basic symptoms was used for the early detection of schizophrenia [147, 242]. Psychological testing catches cognitive disturbances at a more elementary level and can compare the results with norms from the average population. Modern neurocognitive testing offers a very differentiated tool to assess cognitive impairment objectively and reliably and to describe the disturbances in different test-psychological dimensions, whereby the predominant deficits in patients with schizophrenia are in verbal fluency, working memory, executive control, visual memory, mental speed and verbal memory. The inclusion of cognitive impairment in the diagnostic criteria for schizophrenia would enrich the diagnostic concept and hopefully contribute towards a better definition of a 'point of rarity' between schizophrenia and affective psychosis. Indeed, the exclusion of this very relevant core syndrome in research on the differences between schizophrenia and affective psychosis (unipolar and bipolar) [124, 268, 269] might be one explanation why past research on this subject was not so fruitful. The inclusion of the cognitive impairment dimension into the diagnostic criteria for schizophrenia, assessed objectively and reliably by adequate neuropsychological testing, would hopefully lead to another result.

As suggested by Carpenter [56], beside cognitive disturbances DSM-V and ICD-11 should include at least negative symptoms as separate criteria dimensions in addition to positive symptoms. Negative symptoms have been shown to be relevant for prognosis and especially for differentiation between schizophrenia and affective psychosis in the long-term course [203, 210, 285]. In this respect the concept of a 'deficit syndrome' [55], which defines persistent negative symptoms as being an integral part of by schizophrenia and not induced by other factors (depression, extrapyramidal side effects, social withdrawal), would possibly be preferable to the cross-sectional assessment of negative symptoms. It seems to have a clearer association with biological variables [57]. As to drug development, as early as almost two decades ago, when the $5HT_{2A}$ antagonist ritanserin was developed and its efficacy in negative symptoms (but not in positive symptoms) demonstrated [78], the idea arose for the first time that it might be meaningful to develop a drug that targets primarily negative symptoms. Thus, it may be a perspective for the future to develop drugs which primarily act on negative symptoms, possibly without influencing positive symptoms of schizophrenia, if drugs cannot be developed which could influence both dimensions with a sufficient effect size.

Such a syndromatological approach, as an additional descriptive level to a categorial differentiation between schizophrenia and affective disorders or as a primarily syndromatic subclassification of a broad psychosis category in DSM-V or ICD-11, could be a fruitful improvement to our current diagnostic systems. Of course, such a dimensional approach requires that each dimension is covered by adequate assessment procedures and that score values characterise each individual person on the different dimensions. Such a psychometric approach would go far beyond the classical approach in which clinicians describe the existence of syndrome only in qualitative terms.

In addition to giving more weight to cognitive and negative symptoms in the criterial or dimensional description of schizophrenia, it might be necessary to reconsider the relevance of psychiatric symptoms, especially mood-incongruent psychotic symptoms, as a potentially relevant predictor for poor outcome and thus also as a criterion to differentiate schizophrenia from affective psychosis. Based on some follow-up studies, DSM III/IV and ICD-10 have apparently gone too far in including even mood-incongruent psychotic symptoms as a possible part of affective psychoses.

Finally, it should be stated that the long-term course of schizophrenia seems to be more devastating than the long-term course of affective disorders [202], and that some research groups have hypothesised that there might be progressive brain alterations in at least one subgroup of schizophrenic patients [35, 159]. In addition, other neurobiological hypotheses [250] might be good justifications for continuing with the Kraepelinian dichotomy, if a categorical concept of the systematology of psychotic disorders is continued in DSM-V and ICD-11.

The vision for the future would be to construct a psychiatric classification with related brain dysfunctions [251] on a neuroanatomical/neuropathological basis which might be of greater importance in this context then genetic findings [75, 76, 278]. However, a

mixture of both approaches, if possible, may have an even greater impact [255]. At the moment, the idea of constructing a new classification only based on neurobiological parameters without including the clinical features does not seem promising.

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