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The history of bipolar disorders

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Abstract

Bipolar disorders have a long history. Depression and mania are mankind's oldest known mental disorders, and they were the first mental disorders conceptualised by Hippocrates as a part of medicine. Mania and depression as part of one and the same disease – what we today call bipolar disorder – was first described by the famous Greek physician of the first century AD, Aretaeus of Cappadocia.

The next decisive step in the development of our conceptualisation of bipolar disorders was done by two French psychiatrists, Falret (1851) and Baillarger (1854), who described them as separate entities. At the end of the 19th century, Emil Kraepelin subsumed all kinds of mood disorders – both unipolar and bipolar – under the umbrella of manic-depressive insanity. But there was also strong opposition against the very influential opinions of Kraepelin, especially by the so-called Wernicke-Kleist-Leonhard school (Karl Kleist coined the term 'bipolar'), which subclassified bipolar disorders into distinct entities. In 1966, Angst and Perris showed that unipolar and bipolar disorders are autonomous. That was also the start of a very rapid development of concepts, research, and general knowledge about bipolar disorders. Subgroups like cyclothymia, hypomania, and mixed states were identified or re-identified. Another innovation was the development of a bipolar spectrum disorder concept. An overlap of bipolar and schizophrenic spectra can be postulated which is certainly genetically determined, and which gives rise to states like bipolar schizoaffective disorders or acute polymorphic disorders.

Origins: from Homer to Aretaeus

Depression and mania are the oldest known mental disorders of mankind. Depression was the first mental disorder diagnosed by a physician – not by a priest or magician – at least according to Homer. If we accept that the mental disorder of Ajax in the Iliad, which led to his suicide, was an agitated depression, then Podaleirios – the mythic founder of internal medicine and, together with his brother Machaon the surgeon (both were sons of Asklepios), doctors of the Trojan war – diagnosed the 'madness' of Ajax by examining him physically, especially by looking in his eyes.

Independent of the mythic traditions, depression (melancholia) and mania are two of the earliest human disorders scientifically described by Hippocrates and the Hippocratic physicians. Hippocrates assumed a biological basis – namely disturbances or damages of the brain – for depression and mania, but also for hallucinations, delusions, anxiety, etc. [1]: "We suffer all those …

through the brain when it is ill …"[1] (Hippocrates, *On the Sacred Disease*). Although melancholia and mania were known to Greek physicians and philosophers long before, Hippocrates (460–337 BC) was the first to systematically describe them in a scientific way. His book *On the Sacred Disease* could be seen as the beginning not only of scientific medicine in general, but also of psychiatry; he disconnected mental and physical diseases from mysticism, God, and punishment and connected them to physiological processes and to the environment. Mental functions or states like emotions, thinking, perception, volition, and behaviour were – according to Hippocrates – also linked to the brain. Hippocrates based his theories and opinions on the materialistic views of Pythagoras and his scholars, especially Alcmaeon, but also Empedocles. The views of Alcmaeon of Crotona, who may have been the first Greek philosopher and scientist to experiment with animal brains (perhaps at the same time as another great Greek philosopher, Anaxagoras), obviously had a great influence on Hippocrates (see also [2]). Hippocrates was strongly interested in the branch of medical science that about 2200 years later (in 1808 AD) would be named 'psychiatry' by Johann Christian Reil [3], and he was the first to classify mental disorders (into melancholia, mania, hypomania, and paranoia). Together with his fellows (the so-called Hippocratic physicians) he also described organic and toxic deliria, postpartum psychoses, and phobias, and he made the first attempt to describe personalities (choleric, phlegmatic, sanguine, and melancholic personalities) [1, 2].

The term *melancholia* (Greek; 'black bile'; melas = black, cholé = bile) is older than Hippocrates and is based on biological assumptions like that of Alcmaeon, who postulated that the origin of mental disorders was a disturbed interaction of body fluids and the brain, but Hippocrates systematised these views. As a basic characteristic of melancholia, he assumed a long lasting anxiety or fear (Greek: phobos) and moodiness (Greek: dysthymia). Later, Hippocrates as well as Aristotle distinguished between the disease 'melancholia' (Greek: nosos melancholiké) and the corresponding personality type (Greek: typos melancholicós). Whereas the first is a disease, the second is a personality type.

In contrast to the etymology of *melancholia,* that of *mania* is not clear. Even in Homer's time it was associated with several different meanings. The Roman physician Caelius Aurelianus gave at least seven possible etymologies of the Greek word in his book *On Acute Diseases* (translated by Drabkin in 1950). In the classical Greek era four main meanings of the word *mania* were described: 1) a reaction to an event with the meaning of rage, anger, or excitation, e.g., in Homer's Iliad, 2) a biologically defined disease (Hippocrates, Aretaeus of Cappadocia), 3) a divine state (Socrates, Plato), 4) a kind of temperament, especially in its mild form, e.g., hypomania (Hippocrates) [1].

[1] All translations from the Greek by the author of the present paper.

The birth of bipolar disorders

The first to describe mania and melancholia as a bipolar disorder was the Greek physician Aretaeus of Cappadocia in the first century AD. Some of his contemporary physicians had similar views (e.g., Caelius Aurelianus, who himself believed that mania and melancholia did not belong together, but nevertheless cited the contrary views of Apollonius). Aretaeus of Cappadocia was a Greek physician who lived in Alexandria, Egypt in the first century AD. He was the most prominent representative of the 'Eclectics' school of philosophy and was strongly influenced by Hippocrates. In his books *On the Aetiology and Symptomatology of Chronic Diseases* and *The Treatment of Chronic Diseases* he had several chapters on mental disorders like melancholia, mania, phrenitis, and others. He depicts the symptomatology of melancholia as follows: "The symptoms [of melancholia] are not unclear: [the melancholics] either are quiet or dysphoric, sad or apathetic; additionally they could be angry without reason and suddenly awake with panic." In the book *On the Causes and Symptoms of Chronic Diseases* the symptoms of mania were specified as follows: "Some patients with mania are cheerful, they laugh, they play, they dance day and night, they stroll in the market, sometimes with a garland on their heads, as if they had been winner in a game: these patients do not bring worries to their relatives. But others fly into a rage. … The manifestations of mania are countless. Some manics, who are intelligent and well educated, deal with astronomy, although they never have studied it; they deal with philosophy, which they had studied autodidactically; they consider poetry as a gift of muses."

Some authors have claimed that the concept of mania and melancholia as described by Hippocrates, Aretaeus, and other ancient Greek physicians differed from modern concepts. That is not correct. Rather, the classical concepts of melancholia and mania were broader than the modern concepts, but their core is the same [1].

Aretaeus considered melancholia and mania as two manifestations of one and the same disease: "… I think that melancholia is the beginning and a part of mania. … The development of a mania is really a worsening of the disease [melancholia] rather than a change into another disease. … In most of them [melancholics] the sadness disappears after various lengths of time and changes into happiness; the patients then develop a mania."

Resurrection and re-birth of bipolar disorders in modern times

A very long time elapsed between the descriptions of Aretaeus of Cappadocia and new concepts of bipolar disorders. These concepts were put forward 1900 years later by Jean-Pierre Falret [4, 5] and Jules Baillarger [6]. Yet the time between Aretaeus and the two French psychiatrists (Falret and Baillarger) was not empty. Many classical Greek and Roman physicians, such as Asclepiades (who established Greek medicine in Rome), Aurelius Cornelius Celsus (who

translated the most important Greek medical authors into Latin), Soranos of Ephesus, his scholar Caelius Aurelianus, and later Galenos of Pergamos wrote about melancholia, mania, and other mental disorders [1, 2].

Many European authors described (without knowing the work of Aretaeus) the longitudinal association of mania and melancholia, including Willis [7], Morgagni [8], Lorry [9], Heinroth [10], and Griesinger [11, 12] (see also [13, 14]). Then in 1851, Jean-Pierre Falret, a pupil of Esquirol, published a 14-sentence-long statement in the *Gazette des Hôpitaux* ("De la folie circulaire ou forme de maladie mentale caracterisée par l'alternative régulière de la mélancholie"). Falret described for the first time a separate entity, which is characterised by a continuous cycle of depression, mania, and free intervals of varying length and which is different from simple depression. Three years later he completed his concept [5] by defining the sequential change from mania to melancholia and *vice versa* and the interval in between as an independent disease of its own, the 'folie circulaire' [1, 15]. Three years after Falret's first publication, Jules Baillarger [6] described the 'folie à double forme'. Baillarger (arguing very aggressively against Falret) assumed a type of disease in which mania and melancholia change into one another, but the interval is of no importance. In contrast, Falret involved the intervals between the manic and the melancholic episodes in his concept; even episodes of mania and melancholia separated by long intervals belonged together, forming the 'folie circulaire' [1, 15]. The concepts of 'folie circulaire' and 'folie à double forme' found a receptive audience in German-speaking countries [16] as well as in English-speaking countries (as evidenced by publications in *Brain* [17] and in the *American Journal of Insanity* [1, 15, 18]).

At the end of the 19th and beginning of the 20th Centuries it was Emil Kraepelin's fundamental work that strongly influenced psychiatric thinking worldwide. He eliminated the distinction between unipolar and bipolar forms and included all types of mood disorders into the unitary concept of manic-depressive illness, which later proved to be a step back [1, 14, 19–21]. Although Kraepelin himself was non-dogmatic and had severe doubts regarding the validity of his concept [22–24], his followers contributed to some inflexible positions. In his two fundamental works *Die Klinische Stellung der Melancholie* ('The clinical position of melancholia') and the sixth edition of his textbook *Psychiatrie* – both published in 1899 [20, 21] – Kraepelin reported on merging 'circular insanity' and unipolar types as two subtypes of one and the same disorder, namely manic-depressive insanity ('manisch-depressives Irresein'). He wrote: "Unfortunately our textbooks do not help us at all in distinguishing between circular depression and melancholia in cases where the course itself is not informative. The description of melancholic states is absolutely identical to that of circular depression and we can hardly doubt that the most beautiful and exciting descriptions of melancholia are mostly derived from observations of circular cases" [20, p. 328][2]. And some

[2] All translations from the German by the author of the present paper.

pages later: “Apart from our experience that in a whole series of manic episodes a depressive one can occur unexpectedly, and that those cases are immensely rare in which – apart from manic irritability – not the slightest feature of depression is visible, it is absolutely impossible to distinguish these manic fits of circular insanity from periodic mania. But if periodic mania is identical with circular insanity we cannot deny the possibility that also periodic melancholia, or at least some of the cases designated so, must in fact be understood as a kind of circular insanity in which all the episodes take on a depressive hue, just as in periodic mania they all have a manic tinge” [20, p. 333].

In many countries an opposition to Kraepelin’s views arose, but due to his enormous influence this opposition was ignored for many years. Especially the German school of Wernicke, Kleist, and Leonhard delivered subtle descriptions of various affective syndromes, which were assumed to be separate entities. The father of the term ‘bipolar’, Karl Kleist, and his fellow Karl Leonhard, gathered many clinical and family history data to support the distinction between ‘unipolar’ and ‘bipolar’ [25–29].

Unfortunately Kleist’s opinions had no relevant influence on international psychiatry for a long time, at least until 1966, the year of the ‘re-birth’ of bipolar disorders, as Pichot [15] called it. In that year two fundamental studies were published: Jules Angst’s monograph *Zur Ätiologie und Nosologie endogener depressiver Psychosen* (‘On the aetiology and nosology of endogenous depressive psychoses’) [30] and Carlo Perris’s article on *A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses* [31] in a supplement of *Acta Psychiatrica Scandinavica*. The studies of Angst and Perris, which were carried out independently of each other, uncovered very similar findings [32]. They revealed (in summary) that:

1. genetic and peristaltic factors have a synergic impact on the aetiology of ‘endogenous’ depression
2. there is a relationship between female gender and ‘endogenous’ depression; bipolar disorders, however, are equally represented in males and females
3. manic-depressive illness is not homogeneous in a nosological sense. Unipolar depression differs significantly from bipolar disorders in many characteristics
4. unipolar depression has a strong genetic relationship to bipolar disorders.

The work of Angst and Perris, but also that of George Winokur, Paula Clayton, and Theodore Reich [33, 34], showing very similar findings, confirmed some fundamental assumptions of Wernicke, Kleist, and Leonhard and contributed to a real explosion of interest and knowledge in the field of bipolar disorders [14, 35, 36].

Recent developments

In summarising the developments of the last half century it can be pointed out that despite the very dynamic development of biological knowledge about bipolar disorder, which includes genetics and treatment, and which is discussed in various chapters of the present book, the description or re-description of various disorders belonging to a wide bipolar spectrum and their longitudinal course is an essential completion of the concept.

Apart from the classical syndromes of bipolar depression and mania, other special bipolar syndromes were more or less intensely studied: cyclothymia, hypomania, mixed states, bipolar schizoaffective disorder, and other mood disorders or even personality states [37–40].

One of the re-discoveries was that of *cyclothymia*. Cyclothymia is an old and controversial term, first published by Ewald Hecker in 1877 [41], but coined by his teacher Karl Kahlbaum. According to Kahlbaum, 'cyclothymia' refers to the mildest type of bipolar disorders; the term was accepted by Hecker [42] and also by Kraepelin [21]. Ernst Kretschmer [43] described a cyclothymic temperament, and called cyclothymia a "broad constitutional overterm involving health and disease in the same way". The boundaries of cyclothymia as a mood disorder or as a disorder of temperament or personality are not yet clear [37–40].

Another old term, re-discovered in recent years, is *hypomania.* It was, however, first described by Emanuel Mendel in 1881 [44]. Mendel was influenced by Hippocrates, who first described the 'hypomanics' to characterise a type of hyperthymic personality. Mendel wrote: "I recommend (taking under consideration the word used by Hippocrates) to name those types of mania that show a less intense phenomenological picture, 'hypomania'" [44, p. 109]. In recent decades hypomania gained importance through the description of bipolar II disorders by Dunner, Fleiss, and Fieve [45]; through the description of recurrent brief hypomania by Angst [46]; and through its relation to hyperthymic temperament [38]. *Bipolar II disorders*, characterised by episodes of major depression and hypomania, are obviously more frequent than assumed earlier. According to Angst and his co-workers [47] the prevalence of bipolar II disorders amounts to between 5 and 11% of all bipolar disorders, depending on the criteria applied.

In contrast to those mentioned above, the term *rapid cycling* is a modern one. Dunner and Fieve first coined the term in 1974 [48]. Nevertheless, the phenomenon itself was very well known earlier in psychiatry. Emil Kraepelin may have been the first to systematically describe the phenomenon of rapid cycling [21, 49]. The modern term 'rapid cycling', as well as the increasing interest in this phenomenon, has also accrued since the advent of modern, successful psychopharmacological treatments for bipolar disorder. The boundaries between 'rapid cycling' (having at least four cycles in a year) and not 'rapid cycling' (having fewer than four episodes per year) are in fact arbitrary, although Dunner and Fieve found that lithium non-responders tended to

belong to the group of patients who had more than four episodes annually. The subsequent work of Wehr and Goodwin [50] replicated the findings of Dunner and Fieve and additionally anticipated that antidepressant agents could contribute to the manifestation of rapid cycling, a finding that has also been replicated by others [51–53] (see also [54]). The DSM-IV [55] included 'rapid cycling' as a specifier of longitudinal course, but not as a specific mood disorder subtype. The ICD-10 of the World Health Organization [56] does not include any specifier or subgroup 'rapid cycling'.

The *mixed states*, too, have been re-discovered in the 20th century, perhaps under the influence of pharmacotherapy and the recognition of its limitations, especially regarding some sub-groups of bipolar disorders, one of which is the mixed states [35, 57]. The description of mixed states dates back to the very beginning of psychiatry [1], but the German psychiatrist Johann Christian August Heinroth – who was actually the first professor of 'mental medicine' in Europe, perhaps also worldwide – was possibly the first to classify them [10]. He characterised 'mixed states' as a mixture of exaltation and depression (hyper-asthenias) and divided them into three groups, each having four subgroups: 1) 'mixed mood disorders'; 2) 'mixed mental disorders', and 3) 'mixed volition disorders'. The first to conceptualise the mixed states in modern terms were Emil Kraepelin [21] and his pupil Wilhelm Weygandt [58]. Weygandt was also the first to write a book on mixed states in which he concluded: "The co-existence of the main symptoms of both typical episodes of manic-depressive insanity, mostly only of short duration, is extraordinarily frequent; in some cases the mixed states can occupy the entire episode or at least the greater part of its duration; usually the later episodes have the tendency to change to long-lasting mixed states; the course is in many aspects somewhat more chronic than that of the pure manic or depressive episodes, but in other ways the prognosis regarding the recovery of the episode is exactly the same" [58, p. 63].

The renaissance of the study of mixed states began in the USA at the end of the 1970s and the beginning of the 1980s as a consequence of the pharmacological revolution in psychiatry. Initial and relevant contributions were those of Winokur and colleagues [34], Kotin and Goodwin [59], Himmelhoch and colleagues [60, 61], Akiskal and colleagues [62], Akiskal [63–65], Secunda and colleagues [66], Goodwin and Jamison [67], Himmelhoch [68], McElroy and colleagues [69–72], Swann and colleagues [73], and Akiskal and Pinto [74]. Another interesting aspect of the evolution of the mixed states concept is their extension to the group of schizoaffective disorders. But although both ICD-10 and DSM-IV describe a group of 'mixed schizoaffective disorders', there is unfortunately little work on the topic [75, 76]. My colleagues and I have described the frequency, clinical characteristics, and the prognostic value of schizoaffective mixed episodes [35, 77–90]. We have found that mixed states and schizoaffective disorders do not seem to be rare; indeed, approximately 33% of bipolar schizoaffective patients had at least one mixed schizoaffective episode over the long-term course of their illness [57].

One of the most controversial issues of psychiatry concerns *schizoaffective disorders* [91, 92]. Although they seem to be a nosological nuisance for many researchers, they are an everyday reality for every clinician. In this sense they are a challenge for nosologists and other researchers. The nuisance or problem or challenge or reality of the 'intermediate psychotic area' or the 'cases in-between' is even older than the term 'schizoaffective' itself, which was originated by Kasanin in 1933 [14, 91–99], though it may have begun with Karl Kahlbaum [16] and led through Kraepelin's work to the clinical empiricists of the 20th century. The renaissance of schizoaffective disorders also began with the work of Jules Angst in 1966 [30] when he investigated the schizoaffective disorders (under the term 'Mischpsychosen' (mixed psychoses)) as a part of mood disorders. This was an outlier's position not only against the 'zeitgeist', which considered schizoaffective disorders as part of schizophrenia, but was also contrary to the opinion of his teacher Manfred Bleuler, who also assumed they were a part of schizophrenia. Later investigations by Angst and his group [100, 101], by Clayton and colleagues [102], by other members of the Winokur group [103], by Cadoret and colleagues [104], and the voluminous comparative studies of Marneros and co-workers [75, 78–84, 86, 105–111] strongly supported the notion that the relationship between schizoaffective disorder and mood disorders is stronger than the relationship between schizoaffective and schizophrenic disorders.

Schizoaffective disorders can be divided into unipolar and bipolar using the same criteria applied to pure mood disorders. Consequently, bipolar schizoaffective disorders could be assumed to be part of the bipolar spectrum resulting in an overlap of the affective and the schizophrenic spectra [99], and are probably genetically determined [112–114]. Clinical research also provides evidence that the so-called *polymorphic disorders* (acute and transient psychotic disorders) have strong similarities to the bipolar spectrum, building together with schizoaffective disorders a continuum between the bipolar and the schizophrenic spectra [115].

The concept of a spectrum of manic conditions developed by Kretschmer [43] and Eugen Bleuler [116] has undergone various modifications [1, 117]. Over the past decades the group of Jules Angst and Hagop Akiskal provided evidence – based on clinical observations, epidemiological studies, and a sound knowledge of the literature – to establish and enlarge this idea of a continuum [19, 37, 46, 100, 117–122]. The modern concept of a bipolar spectrum includes variations of overlapping temperament, personality, and clinical picture in the affective and schizophrenic spectra [99]. Bipolar schizoaffective disorders, as well as acute and transient psychotic disorders – especially the acute polymorphic psychoses (the so-called 'cycloid psychoses' of Wernicke, Kleist, and Leonhard or the 'Bouffée délirante' of Magnan) – may be the most important clinical manifestations of a genetically determined overlap of schizophrenic and affective spectra [113, 114], as shown in Figure 1.

Finally, the history of the treatment of bipolar disorders is the history of treatment in psychiatry. The physical therapies devised by Greek and Roman

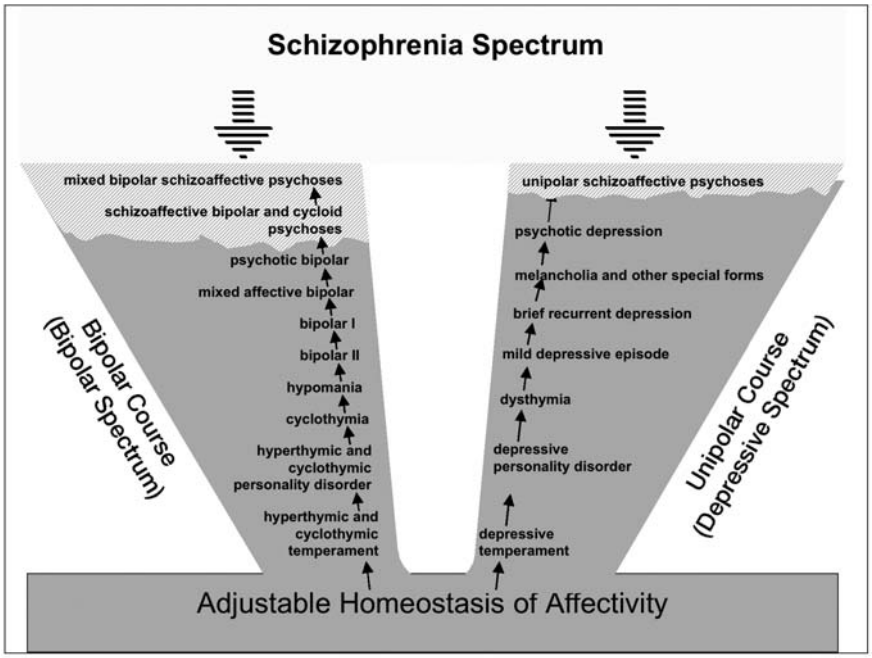

Figure 1. The severity spectrum of mood disorders (adopted from [88]).

physicians were applied with fewer or more modifications up to the end of the 19th century. Phytopharmacotherapy, insulin, cardiazol, electroconvulsive treatment, opium, alcoholic beverages, narcotics (already used by the Greeks), bromides, chloral hydrates, rauwolfia serpentina, and other drugs were still used in the 20th century until the development of modern psychopharmacology [2]. The psychopharmacological revolution in psychiatry began in the second half of the 20th century and had an enormous impact on all areas of psychiatric knowledge. This topic, however, is beyond the scope of this chapter.

References

1 Marneros A, Angst J (2000) Bipolar disorders: roots and evolution. In: A Marneros, J Angst (eds): *Bipolar Disorders*. Kluwer Academic Publishers, Dordrecht, Boston, London, 1–36
2 Alexander F, Selesnick S (1966) *The history of psychiatry*. Harper & Row, New York
3 Marneros A, Pillmann F (2005) *Das Wort Psychiatrie wurde in Halle geboren*. Schattauer, Stuttgart
4 Falret J (1851) De la folie circulaire ou forme de maladie mentale caracterisée par l'alternative régulière de la manie et de la mélancolie. *Bull Acad Natl Med (Paris)*
5 Falret J (1854) Mémoire sur la folie circulaire, forme de maladie mentale caracterisée par la reproduction successive et régulière de l'état maniaque, de l'état mélancholique, et d'un intervalle lucide plus ou moins prolongé. *Bull Acad Natl Med (Paris)* 382–415
6 Baillarger J (1854) De la folie à double forme. *Ann méd psychol* 6

7 Willis T (1676) *De anima brutorum*. Lyon
8 Morgagni JB (1761) *Recherches anatomiques sur le siège et les causes des maladies (translated)*. Destouet, Venice
9 Lorry AC (1765) *De melancholia et morbis melancholis*. Paris
10 Heinroth JCA (1818) *Lehrbuch der Störungen des Seelenlebens oder der Seelenstörung und ihrer Behandlung – aus rationaler Sicht*. Vogel, Leipzig
11 Griesinger W (1845) *Pathologie und Therapie der psychischen Krankheiten*. Krabbe, Stuttgart
12 Griesinger W (1861) *Pathologie und Therapie der psychischen Krankheiten, 2nd edition*. Krabbe, Stuttgart
13 Haugsten TH (1995) Les troubles bipolaires dans l'histoire de la psychiatrie (Kraepelin excepté). In: ML Bourgeois, H Verdoux (eds): *Les troubles bipolaires de l'humeur*. Masson Médicine et Physiotherapie, Paris
14 Marneros A, Angst J (2000) *Bipolar Disorders. 100 Years after manic depressive insanity*. Kluwer Academic Publishers, Dordrecht, Boston, London
15 Pichot P (1995) The birth of the bipolar disorder. *Eur Psychiatry* 10: 1–10
16 Kahlbaum K (1863) *Die Gruppirung der psychischen Krankheiten und die Eintheilung der Seelenstörungen*. Kafemann, Danzig
17 Foville A (1882) Folie à double forme. *Brain* 5: 288–323
18 Hurd HM (1882) The treatment of periodic insanity. *Am J Insanity* 39: 174–180
19 Angst J (1997) A brief history of bipolar disorder. *J Bipolar Disord* 1: 31–36
20 Kraepelin E (1899) Die klinische Stellung der Melancholie. *Mschr Psychiatr Neurol* 6: 325–335
21 Kraepelin E (1899) *Psychiatry. 6th edition*. Barth, Leipzig
22 Kraepelin E (1920) Die Erscheinungsformen des Irreseins. *Zeitschrift für die gesamte Neurologie und Psychiatrie* 62: 1–29
23 Craddock N, Owen MJ (2007) Rethinking psychosis: the disadvantages of a dichotomous classification now outweigh the advantages. *World Psychiatry* 6: 20–27
24 Marneros A (2006) Beyond the Kraepelinian dichotomy: acute and transient psychotic disorders and the necessity for clinical differentiation. *Br J Psychiatry* 189: 1–2
25 Kleist K (1911) Die klinische Stellung der Motilitätspsychosen. *Z Gesamte Neurol Psychiatr* 3: 914–977
26 Kleist K (1926) Über cycloide Degenerationspsychosen, besonders Verwirrtheits – und Motilitätspsychosen. *Zentralblatt für die gesamte Neurologie und Psychiatrie* 44: 655–657
27 Kleist K (1928) Über cycloide, paranoide und epileptoide Psychosen und über die Frage der Degenerationspsychosen. *Schweizer Archiv für Neurologie, Neurochirurgie und Psychiatrie* 23: 3–37
28 Kleist K (1953) Die Gliederung der neuropsychischen Erkrankungen. *Mon Psychiatrie Neurol* 125: 526–554
29 Leonhard K (1957) *Die Aufteilung der endogenen Psychosen*. Akademie-Verlag, Berlin
30 Angst J (1966) *Zur Ätiologie und Nosologie endogener depressiver Psychosen. Eine genetische, soziologische und klinische Studie*. Springer, Berlin, Heidelberg, New York
31 Perris C (1966) A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses. *Acta Psychiatr Scand* 194 (suppl): 1–89
32 Angst J, Perris C (1968) Zur Nosologie endogener Depressionen. Vergleich der Ergebnisse zweier Untersuchungen. *Arch Psychiatrie Z Neurol* 373–386
33 Winokur G, Clayton P (1967) Family history studies: I. Two types of affective disorders separated according to genetic and clinical factors. In: J Wortis (ed.): *Recent advances in Biological Psychiatry. Vol. 10*. Plenum, New York
34 Winokur G, Clayton PJ, Reich T (1969) *Manic Depressive Illness*. CV Mosby, St Louis
35 Marneros A, Goodwin FK (2005) *Bipolar Disorders. Mixed States, Rapid Cycling and Atypical Forms*. Cambridge University Press, Cambridge
36 Goodwin FK, Jamison KR (2007) *Manic-depressive Illness. Bipolar Disorders and Recurrent Depression*. Oxford University Press, Oxford
37 Akiskal HS (1983) Dysthymic and cyclothymic disorders: a paradigm for high risk research. In: JM Davis, JW Maas (eds): *The Affective Disorders*. American Psychiatric Press, Washington, DC, 211–231
38 Akiskal HS, Akiskal K (1992) Cyclothymic, hyperthymic, and depressive temperaments as subaffective variants of mood disorders. In: A Tasman, MB Riba (eds): *Review of Psychiatry 11*. American Psychiatric Press, Washington, DC

39 Akiskal HS, Chen SE, Davis GC, Puzantian VR, Kashgarian M, Bolinger JM (1985) Borderline: an adjective in search of a noun. *J Clin Psychiatry* 46: 41–48
40 Akiskal HS, Maser JD, Zeller PJ, Endicott J, Coryell W, Keller M, Warshaw M, Clayton P, Goodwin F (1995) Switching from 'unipolar' to bipolar II. An 11-year prospective study of clinical and temperamental predictors in 559 patients. *Arch Gen Psychiatry* 52: 114–123
41 Hecker E (1877) Zur klinischen Diagnostik und Prognostik der psychischen Krankheiten. *Allg Z Psychiatrie* 33: 602–620
42 Hecker E (1898) Die Cyclothymie, eine cirkuläre Gemüthserkrankung. *Z Prakt Ärzte* 7: 6–15
43 Kretschmer E (1921–1950) *Körperbau und Charakter (1st–21st edition)*. Springer, Berlin
44 Mendel E (1881) *Die Manie*. Urban & Schwarzenberg, Wien, Leipzig
45 Dunner DL, Fleiss JL, Fieve RR (1976) The course of development of mania in patients with recurrent depression. *Am J Psychiatry* 133: 905–908
46 Angst J (1997) Recurrent brief psychiatric syndromes: Hypomania, depression, anxiety and neurasthenia. In: LL Judd, B Saletu, V Filip (eds): *Basic and clinical science of mental and addictive disorders*. Karger, Basel
47 Angst J, Gamma A, Ajdacic V, Eich D, Pezawas L, Rössler W (2005) Recurrent brief depression as an indicator of severe mood disorders. In: A Marneros, FK Goodwin (eds): *Bipolar Disorders. Mixed States, Rapid Cycling and Atypical Forms*. Cambridge University Press, Cambridge, 109–130
48 Dunner DL, Fieve RR (1974) Clinical factors in lithium carbonate prophylaxis failure. *Arch Gen Psychiatry* 30: 229–233
49 Kraepelin E (1913) *Psychiatrie. Ein Lehrbuch für Studierende und Ärzte. 3rd volume: Klinische Psychiatrie, 2nd part (8th edition).* Johann Ambrosius Barth, Leipzig
50 Wehr TA, Goodwin F (1979) Rapid cycling in manic-depressives induced by tricyclic antidepressants. *Arch Gen Psychiatry* 36: 555–559
51 Calabrese JR, Meltzer HY, Markovitz PJ (1991) Clozapine prophylaxis in rapid cycling bipolar disorder. *J Clin Psychopharmacol* 11: 396–397
52 Calabrese JR, Woyshville MJ, Kimmel SE, Rapport DJ (1993) Predictors of valproate response in bipolar rapid cycling. *J Clin Psychopharmacol* 13: 280–283
53 Elhaj O, Calabrese JR (2005) Rapid-cycling bipolar disorder. In: A Marneros, FK Goodwin (eds): *Bipolar Disorders. Mixed States, Rapid Cycling and Atypical Forms*. Cambridge University Press, Cambridge, 61–87
54 Kilzieh N, Akiskal HS (1999) Rapid-cycling bipolar disorder. An overview of research and clinical experience. *Psychiatr Clin North Am* 22: 585–607
55 APA (1994) *Diagnostic and Statistical Manual of Mental Disorders. 4th edition. (DSM-IV).* American Psychiatric Association, Washington
56 WHO (1991) *ICD-10 Classification of Mental and Behavioural Disorders*. Churchill Livingstone, Edinburgh, London, Melbourne, New York, Tokyo
57 Marneros A, Goodwin FK (2005) Bipolar disorders beyond major depression and euphoric mania. In: A Marneros, FK Goodwin (eds): *Bipolar Disorders. Mixed States, Rapid Cycling and Atypical Forms*. Cambridge University Press, Cambridge, 1–44
58 Weygandt W (1899) *Über die Mischzustände des manisch-depressiven Irreseins*. JF Lehmann, München
59 Kotin J, Goodwin F (1972) Depression during mania: clinical observations and theoretical observations. *Am J Psychiatry* 129: 55–56
60 Himmelhoch JM, Coble P, Kupfer KJ, Ingenito J (1976) Agitated psychotic depression associated with severe hypomanic episodes: a rare syndrome. *Am J Psychiatry* 133: 765–771
61 Himmelhoch JM, Mulla D, Neil JF, Detre TP, Kupfer DJ (1976) Incidence and significance of mixed affective states in a bipolar population. *Arch Gen Psychiatry* 33: 1062–1066
62 Akiskal HS, Khani MK, Scott-Strauss A (1979) Cyclothymic temperament disorders. *Psychiatr Clin North Am* 2: 527–554
63 Akiskal H (1981) Subaffective disorders: dysthymic, cyclothymic and bipolar II disorders in the "border-line" realm. *Clin North Am* 4: 25–46
64 Akiskal H (1992) The mixed states of bipolar I, II, III. *Clin Neuropsychopharm* 15: 632–633
65 Akiskal H (1997) Overview of chronic depressions and their clinical management. In: H Akiskal, G Cassano (eds): *Dysthymia and the spectrum of chronic depressions*. Guilford Press, New York, 1–34
66 Secunda SK, Swann A, Katz MM, Koslow SH, Croughan J, Chang S (1987) Diagnosis and treat-

ment of mixed mania. *Am J Psychiatry* 144: 96–98
67 Goodwin FK, Jamison KR (1990) *Manic-Depressive Illness*. Oxford University Press, Oxford
68 Himmelhoch JM (1992) The sources of characterologic presentations of mixed bipolar states. *Clin Neuropsychopharm* 15: 630A–631A
69 McElroy SL, Freeman MP, Akiskal H (2000) The mixed bipolar disorder. In: A Marneros, J Angst (eds): *Bipolar Disorders. 100 years after manic depressive insanity*. Kluwer Academic Publishers, Dordrecht, 63–88
70 McElroy SL, Keck PE Jr, Pope HG Jr, Hudson JI, Faedda GL, Swann AC (1992) Clinical and research implications of the diagnosis of dysphoric or mixed mania or hypomania. *Am J Psychiatry* 149: 1633–1644
71 McElroy SL, Strakowski SM, Keck PE Jr, Tugrul KL, West SA, Lonczak HS (1995) Differences and similarities in mixed and pure mania. *Compr Psychiatry* 36: 187–194
72 McElroy SL, Strakowski SM, West SA, Keck PE Jr, McConville BJ (1997) Phenomenology of adolescent and adult mania in hospitalized patients with bipolar disorder. *Am J Psychiatry* 154: 44–49
73 Swann A, Secunda SK, Katz MM (1995) Specifity of mixed affective states: clinical comparison of dysphoric mania and agitated depression. *J Clin Psychiatry* 56: 6–10
74 Akiskal HS, Pinto O (2000) The soft bipolar spectrum: footnotes to Kraepelin on the interface of hypomania, temperament and depression. In: A Marneros, J Angst (eds): *Bipolar Disorders. 100 Years after Manic-depressive Insanity*. Kluwer, Dordrecht, Boston, London, 37–62
75 Marneros A, Röttig S, Wenzel A, Blöink R, Brieger P (2005) Schizoaffective mixed states. In: A Marneros, FK Goodwin (eds): *Bipolar Disorders. Mixed States, Rapid Cycling and Atypical Forms*. Cambridge University Press, Cambridge, 187–206
76 Marneros A, Rottig S, Wenzel A, Bloink R, Brieger P (2004) Affective and schizoaffective mixed states. *Eur Arch Psychiatry Clin Neurosci* 254: 76–81
77 Marneros A (1989) *Schizoaffektive Psychosen. Diagnose, Therapie und Prophylaxe*. Springer, Berlin, Heidelberg, New York
78 Marneros A, Deister A, Rohde A (1986) The Cologne Study on schizoaffective disorders and schizophrenia suspecta. In: A Marneros, MT Tsuang (eds): *Schizoaffective Psychoses*. Springer, Berlin, Heidelberg, New York, 123–142
79 Marneros A, Deister A, Rohde A, Junemann H, Fimmers R (1988) Long-term course of schizoaffective disorders. Part I: Definitions, methods, frequency of episodes and cycles. *Eur Arch Psychiatry Neurol Sci* 237: 264–275
80 Marneros A, Rohde A, Deister A, Fimmers R, Junemann H (1988) Long-term course of schizoaffective disorders. Part III: Onset, type of episodes and syndrome shift, precipitating factors, suicidality, seasonality, inactivity of illness, and outcome. *Eur Arch Psychiatry Neurol Sci* 237: 283–290
81 Marneros A, Rohde A, Deister A, Junemann H, Fimmers R (1988) Long-term course of schizoaffective disorders. Part II: Length of cycles, episodes, and intervals. *Eur Arch Psychiatry Neurol Sci* 237: 276–282
82 Marneros A, Deister A, Rohde A (1989) Unipolar and bipolar schizoaffective disorders: a comparative study. I. Premorbid and sociodemographic features. *Eur Arch Psychiatry Neurol Sci* 239: 158–163
83 Marneros A, Deister A, Rohde A, Junemann H (1989) Unipolar and bipolar schizoaffective disorders: a comparative study. III. Long-term outcome. *Eur Arch Psychiatry Neurol Sci* 239: 171–176
84 Marneros A, Rohde A, Deister A (1989) Unipolar and bipolar schizoaffective disorders: a comparative study. II. Long-term course. *Eur Arch Psychiatry Neurol Sci* 239: 164–170
85 Marneros A, Andreasen NC, Tsuang MT (1991) *Negative versus Positive Schizophrenia*. Springer, Berlin, Heidelberg, New York
86 Marneros A, Deister A, Rohde A (1991) *Affektive, Schizoaffektive und Schizophrene Psychosen: Eine vergleichende Langzeitstudie*. Springer, Berlin, Heidelberg, New York
87 Marneros A, Deister A, Rohde A (2000) Bipolar schizoaffective disorders. In: A Marneros, J Angst (eds): *Bipolar Disorders: 100 years after manic depressive insanity*. Kluwer Academic Publishers, Dordrecht, 111–126
88 Marneros A (2004) *Das Neue Handbuch der Bipolaren und Depressiven Erkrankungen*. Thieme, Stuttgart, New York
89 Marneros A, Rohde A, Deister A (1996) Bipolar mixed illness. *Eur Neuropsychopharmacol* 6: 9
90 Marneros A, Rohde A, Deister A, Fischer J (1996) Die gemisch-bipolare Erkrankung. *Nervenarzt* 67: 67

91 Maj M (1984) The evolution of some European diagnostic concepts relevant to the category of schizoaffective psychoses. *Psychopathology* 17: 158–167
92 Marneros A, Tsuang MT (1986) *Schizoaffective Psychoses*. Springer, Berlin, Heidelberg, New York
93 Kasanin J (1933) The acute schizoaffective psychoses. *Am J Psychiatry* 13: 97–126
94 Angst J (1986) The course of schizoaffective disorders. In: A Marneros, MT Tsuang (eds): *Schizoaffective Psychoses*. Springer, Berlin, Heidelberg, New York, 63–93
95 Perris C (1986) The case for the independence of cycloid psychotic disorder from the schizoaffective disorders. In: A Marneros, MT Tsuang (eds): *Schizoaffective Psychoses*. Springer, Berlin, Heidelberg, New York, 272–308
96 Pichot P (1986) A comparison of different national concepts of schizoaffective psychosis. In: A Marneros, MT Tsuang (eds): *Schizoaffective Psychoses*. Springer, Berlin, Heidelberg, New York, 8–17
97 Strömgren E (1986) Reactive (psychogenic) psychoses and their relations to schizoaffective psychoses. In: A Marneros, MT Tsuang (eds): *Schizoaffective Psychoses*. Springer, Berlin, Heidelberg, New York, 260–271
98 Angst J, Marneros A (2001) Bipolarity from ancient to modern times: conception, birth and rebirth. *J Affect Disord* 67: 3–19
99 Marneros A, Akiskal HS (2007) *The Overlap of Affective and Schizophrenic Spectra.* Cambridge University Press, Cambridge
100 Angst J (1990) Recurrent brief depression: a new concept of depression. *Pharmacopsychiatry* 23: 63–66
101 Angst J (1989) Der Verlauf schizoaffektiver Psychosen. In: A Marneros (eds): *Schizoaffektive Psychosen, Diagnose, Therapie und Prophylaxe*. Springer, Berlin, 87–88
102 Clayton P (1968) Family history studies: III – Schizoaffective disorder, clinical and genetic factors – including a one to two year follow-up. *Compr Psychiatry* 9: 31–49
103 Fowler RC, McCabe MS, Cadoret RJ, Winokur G (1972) The validity of good prognosis schizophrenia. *Arch Gen Psychiatry* 26: 182–185
104 Cadoret RJ, Fowler RC, McCabe MS, Winokur G (1974) Evidence for heterogeneity in a group of good-prognosis schizophrenics. *Compr Psychiatry* 15: 443–450
105 Marneros A, Rohde A, Deister A (1986) Features of schizoaffective disorders: The "cases-in-between". In: A Marneros, MT Tsuang (eds): *Schizoaffective Psychoses*. Springer, Berlin, Heidelberg, New York, 143–154
106 Marneros A, Rohde A, Deister A, Risse A (1986) Schizoaffective disorders: The prognostic value of the affective component. In: A Marneros, MT Tsuang (eds): *Schizoaffective Psychoses*. Springer, Berlin, Heidelberg, New York, 155–163
107 Marneros A, Deister A, Rohde A, Steinmeyer EM, Junemann H (1989) Long-term outcome of schizoaffective and schizophrenic disorders: a comparative study. I. Definitions, methods, psychopathological and social outcome. *Eur Arch Psychiatry Neurol Sci* 238: 118–125
108 Marneros A, Steinmeyer EM, Deister A, Rohde A, Junemann H (1989) Long-term outcome of schizoaffective and schizophrenic disorders: a comparative study. III. Social consequences. *Eur Arch Psychiatry Neurol Sci* 238: 135–139
109 Steinmeyer EM, Marneros A, Deister A, Rohde A, Junemann H (1989) Long-term outcome of schizoaffective and schizophrenic disorders: a comparative study. II. Causal-analytical investigations. *Eur Arch Psychiatry Neurol Sci* 238: 126–134
110 Marneros A (2007) The paradigma of overlapping affective and schizophrenic spectra: schizoaffective conditions. In: A Marneros, HS Akiskal (eds): *The Overlap of Affective and Schizophrenic Spectra*. Cambridge University Press, Cambridge, 1–24
111 Marneros A, Röttig S, Röttig D, Tscharntke A, Brieger P (2007) The longitudinal polymorphism of bipolar I disorders and its theoretical implications. *J Affective Disord* 107: 117–126
112 Craddock N, O'Donovan MC, Owen MJ (2005) The genetics of schizophrenia and bipolar disorder: dissecting psychosis. *J Med Genet* 42: 193–204
113 Craddock N, O'Donovan MC, Owen MJ (2007) Phenotypic and genetic complexity of psychosis. *Br J Psychiatry* 190: 200–203
114 Kelsoe JR (2007) The overlapping of the spectra: overlapping genes and genetic models. In: A Marneros, HS Akiskal (eds): *The Overlap of Affective and Schizophrenic Spectra*. Cambridge University Press, Cambridge, 25–42
115 Marneros A, Pillmann F (2004) *Acute and Transient Psychoses*. Cambridge University Press,

Cambridge
116 Bleuler E (1922) Die Probleme der Schizoidie und der Syntonie. *Z Gesamte Neurol Psychiatr* 78
117 Akiskal HS (2002) Classification, diagnosis and boundaries of bipolar disorders: a review. In: M Maj, H Akiskal, JJ Lopez-Ibor, N Sartorius (eds): *Bipolar Disorder*. Wiley & Sons, Chichester, 1–52
118 Angst J (1997) Minor and recurrent brief depression. In: HS Akiskal, GB Cassano (eds): *Dysthymia and the spectrum of chronic depression*. Guilford, New York, London
119 Angst J (2008) The affective spectrum and its neglected sub-diagnostic groups. In: A Marneros, D Röttig (eds): *Biogenese und Psychogenese*. Roderer, Regensburg
120 Akiskal HS (1983) Dysthymic disorder: psychopathology of proposed chronic depressive subtypes. *Am J Psychiatry* 140: 11–20
121 Akiskal HS, Mallya G (1987) Criteria for the 'soft' bipolar spectrum: treatment implications. *Psychopharmacol Bull* 23: 68–73
122 Akiskal HS, Djenderedjian AM, Rosenthal RH, Khani MK (1977) Cyclothymic disorder: validating criteria for inclusion in the bipolar affective group. *Am J Psychiatry* 134: 1227–1233