

Millennial article

Bipolarity from ancient to modern times: conception, birth and rebirth

Jules Angst^a, Andreas Marneros^{b,*}

^a*Department of Psychiatry, University of Zürich, Zurich, Switzerland*

^b*Department of Psychiatry and Psychotherapy, Martin-Luther University Halle-Wittenberg, 06097 Halle, Germany*

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Abstract

We review the history of bipolar disorders from the classical Greek period to DSM-IV. Perhaps the first person who described mania and melancholia as two different phenomenological states of one and the same disease was the Greek physician of the 1st century AD, Aretaeus of Cappadocia. The modern concept of bipolar disorders was born in France, with the publications of Falret (1851) and Baillarger (1854). Emil Kraepelin, however, in 1899, unified all types of affective disorders in 'manic-depressive insanity'; in spite of some opposition, Kraepelin's unitary concept was adopted worldwide. In the 1960s, however, the rebirth of bipolar disorders took place through the publications of Jules Angst, Carlo Perris, and George Winokur, who independently showed that there exist clinical, familial and course characteristics validating the distinction between unipolar and bipolar disorders; in addition, they verified several of the corresponding opinions of the Wernicke-Kleist-Leonhard school. The concept of unipolar and bipolar disorders has further advanced in the last three decades: landmark developments include the renaissance of Kraepelin's mixed states and of Kahlbaum's and Hecker's cyclothymia and related affective temperaments, the concept of soft bipolar spectrum (Akiskal), and the distinction of schizoaffective disorders into unipolar and bipolar forms. © 2001 Published by Elsevier Science B.V.

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1. The classical period

The origin of the concept of bipolar disorders has its roots in the work and views of the Greek physicians of the classical period. Mania and melan-

cholia are two of the earliest described human diseases. Morbid states of depression and exaltation were known to the physicians and philosophers of the pre-Hippocratic era. Heroes in the poems of Homer were used by ancient Greek physicians and philosophers (e.g. Aristoteles (1962, 1991) and Aretaeus of Cappadocia (1847)) as examples of mania or melancholia. Hippocrates (460–337 BC), however, was the first who systematically described mania and melancholia. Hippocrates based his work

*Corresponding author. Tel.: +49-345-557-3651; fax: +49-345-557-3607.

E-mail address: andreas.marneros@medizin.uni-halle.de (A. Marneros).

on the materialistic views of Pythagoras and his scholars Alcmaeon and Empedocles of Crotona. Alcmaeon may have been the first Greek philosopher and scientist who experimented with the brains of animals (Anaxagoras may have done so around the same time, 500–400 BC). Alcmaeon tried to find auditory and visual channels to the brain. He thought that the origin of diseases was the disturbed interaction of body fluids with the brain. Alcmaeon's work 'On Nature' was probably the most fundamental text used by pre-Hippocratic writers (Alexander and Selesnick, 1966).

Hippocrates supplemented such theories with excellent bedside observations as well as longitudinal follow-up. Psychiatry was one of Hippocrates' main interests and he formulated the first classification of mental disorders, namely melancholia, mania and paranoia (Hippokrates, 1897). Hippocratic physicians also described organic and toxic deliria, postpartum psychoses and phobias, and coined the term 'hysteria'. Furthermore, they made the first attempts to describe personality in terms of their humoral theories dividing the different types of personality into choleric, phlegmatic, sanguine and melancholic (Erich Mendel reactivated Hippocrates' term 'hypo-mania' in 1881). Hippocrates and his school, though strictly biologists, pointed out the relevance for disease (including mental disease) of biography and of the social and topographical environment as well as the significance of a strong relationship between physician and patient (Marneros, 1999). Hippocrates assumed the brain as the organ of mental functions, mental disturbances and mental disorders. In his famous work 'On the Sacred Disease' (i.e. epilepsy) he wrote:

"The people ought to know that the brain is the sole origin of pleasures and joys, laughter and jests, sadness and worry as well as dysphoria and crying. Through the brain we can think, see, hear and differentiate between feeling ashamed, good, bad, happy ... Through the brain we become insane, enraged, we develop anxiety and fears, which can come in the night or during the day, we suffer from sleeplessness, we make mistakes and have unfounded worries, we lose the ability to recognize reality, we become apathetic and we cannot participate in social life ... We suffer all

those mentioned above through the brain when it is ill ..."¹.

Although the etymology of the term 'melancholia' is clear, the origin of 'mania' is less so, because of its roots in the mythological area. 'Melancholia' ('melas' means black, and 'cholé' means bile) was based on the humoral theories of Alcmaeon of Crotona and the pre-Hippocratic Greek physicians who explained psychopathological states of severe sadness and other mental disorders with an interaction of body liquids, especially bile, and the brain. Later Hippocrates, as well as Aristotle, distinguished between the disease 'melancholia' (nosos melancholiké) and the corresponding personality type (typos melancholicós). The etymology of 'mania' is difficult in that the word has a lot of meanings. It was used in mythology and poems (e.g. like those of Homer) to describe different states. The Roman physician Caelius Aurelianus, a member of the Methodist School and a student of Soranus of Ephesus, gave in his book 'On Acute Diseases' (Chapter V) at least seven possible etymologies. He wrote:

"The school of Empedocles holds that one form of madness consists in a purification of the soul, and the other in an impairment of the reason resulting from a bodily disease or indisposition. It is this latter form that we shall now consider. The Greeks call it *mania* because it produces great mental anguish (Greek *ania*); or else because there is excessive relaxing of the soul or mind, the Greek word for 'relaxed' or 'loose' being *manos*; or because the disease defiles the patient, the Greek word 'to defile' being *lymaenein*; or because it makes the patient desirous of being alone and in solitude, the Greek word 'to be bereft' and 'to seek solitude' being *monusthae*; or because the disease holds the body tenaciously and is not easily shaken off, the Greek word for 'persistence' being *monia*; or because it makes the patient hard and enduring (Greek *hypomeneticos*)."¹ (Caelius Aurelianus, translated by Drabkin, 1950).

¹Translation of original Greek and German quotations by Andreas Marneros.

In the classical era four meanings of ‘mania’ were described:

1. A reaction to an event with the meaning of rage, anger or excitation (like Homer in his Iliad who described ‘Aias maenomenos’, meaning ‘Ajax in a rage’)
2. A biologically defined disease (Hippocrates, Aretaeus of Cappadocia and others)
3. A divine state (Socrates, Plato)
4. A kind of temperament, especially in its mild form (Hippocrates)

Caelius Aurelianus wrote in his book on chronic diseases:

“In the Phaedrus, Plato declares that there are two kinds of mania, one involving a mental strain that arises from a bodily cause of origin, the other divine or inspired, with Apollo as the source of the inspiration. This latter kind, he says, is now called ‘divination’, but in early times was called ‘madness’; that is, the Greeks now call it ‘prophetic inspiration’ (*mantice*), though in remote antiquity it was called ‘mania’. Plato goes on to say that another kind of divine mania is sent by Father Bacchus, that still another, called ‘erotic inspiration’, is sent by the god of love and that a fourth kind comes from the Muses and is called ‘protreptic inspiration’ because it seems to inspire men to song. The Stoics also say that madness is of two kinds, but they hold that one kind consists in lack of wisdom, so that they consider every imprudent person mad; the other kind, they say, involves a loss of reason and a concomitant bodily affection.” (Caelius Aurelianus, translated by Drabkin, 1950).

The views of Empedocles regarding the meanings of the term ‘mania’ have been cited above. But when Socrates, in Plato’s Phaidros (Phaedrus) said: “The highest of all good things are given to us by the mania” (Platon, 1991), he certainly meant the ‘divine mania’, and also creativity in some states which today will be called ‘hypomania’ or ‘hyperthymia’ or ‘hyperthymic temperament’ (as Jamison (1994) shows in her book ‘Touched with Fire’). But the Greeks also associated melancholia, especially

melancholic personality, with genius and creativity. Aristotle asked in his book ‘Problemata physica’:

“ ‘Why are extraordinary men in philosophy, politics or the arts melancholics?’ Hippocrates himself discussed after examining the famous ‘atomical’ philosopher Democritus and after exciting discussions with him, the connection between melancholia and genius. He addressed to the citizens of Abdira the happy message that their fellow citizen Democritus suffered not from melancholia but he is simply a genius” (Temkin, 1985).

Some authors have claimed that the concept of mania and melancholia as described by Hippocrates, Aretaeus and other ancient Greek physicians is different from the modern concepts (Ackerknecht, 1959), but this is not correct. Rather, the classical concepts of melancholia and mania were broader than modern concepts (they included melancholia or mania, mixed states, schizoaffective disorders, some types of schizophrenia and some types of acute organic psychoses and ‘atypical’ psychoses; Marneros, 1999).

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), Soranus of Ephesus and his scholar Caelius Aurelianus (who wrote down the views of his teacher, extensively on phrenitis, mania and melancholia), and later Galenus of Pergamos, focussed their interest on mental disorders, especially melancholia and mania (Fischer-Homberger, 1968; Alexander and Selesnick, 1966). However, principally it was Aretaeus of Cappadocia who most explicitly described the intimate link between them.

2. Aretaeus of Cappadocia

Aretaeus of Cappadocia lived in Alexandria in the 1st century AD (his dates of birth and death are not known: some authors say he lived from ~30 to 90 AD, others from 50 to 130 AD). Aretaeus is the most prominent representative of the ‘Eclectics’. The Eclectics were strongly influenced by Hippocrates

and they were so called because they were not bound by any systems of therapy. Eclecticism meant choosing the best from many sources, a meaning it still has today, especially in psychotherapy. Aretaeus was very careful in his description of diseases (Aretaeus of Cappadocia, 1847) and he favored observations of details. He was free of dogma and superstition. In his books ‘On the Aetiology and Symptomatology of Chronic Diseases’ and ‘The Treatment of Chronic Diseases’ he described mental disorders very carefully. Chapter V in the former book addresses melancholia, and Chapter VI mania. Mental disorders are, according to Aretaeus (in agreement with Hippocrates), biological in cause, but he differentiated between a biologically caused melancholia and a psychologically caused ‘reactive depression’. He wrote in Chapter V:

“It has been reported about a man who had been assumed to suffer from an incurable melancholia, and the physicians were not able to help him. But the love of a young girl was able to cure him. In my opinion he was always in love with her but because he thought that she did not have any interest in him he became dysphoric and sad, so that he suffered from melancholia. But he did not express his feelings to the girl. When he did so, and the girl responded, his sadness, dysphoria and anger disappeared and he became happy. In this sense love was the physician”.

Aretaeus was the first to explicitly link mania and melancholia (Marneros, 1999). Of his contemporaries, Caelius Aurelianus, though against the view that mania and melancholia belong together, nonetheless cited Apollonius, who believed the two affective states were related. Aretaeus conceived mania and melancholia as two different images of one single disease. In Chapter V of ‘On the Aetiology and Symptomatology of Chronic Diseases’ he says:

“... 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 became better after various lengths of time and

changed into happiness; the patients then developed a mania”.

The position of Aretaeus, as described in his two books, can be summarized as following (Marneros, 1999):

1. Melancholia and mania have the same aetiology, namely disturbances of the function of the brain and some other organs.
2. Mania is a worsening of melancholia.
3. Mania is the phenomenological counterpart of melancholia.
4. His concepts of melancholia and mania were broader than the modern concepts: depression, psychotic depression, schizoaffective disorders, mixed states, schizophrenia with affective symptomatology and some organic psychoses were involved.
5. He differentiated between melancholia, which is a biologically caused disease, and reactive depression, a psychologically caused state.

In brief, although Aretaeus’ views on affective states were broader than what today we call bipolar disorder, his connection of mania and melancholia can be justifiably considered the first conception of bipolarity.

3. From Aretaeus to Jean-Pierre Falret

The change from mania to melancholia and vice versa was also noted by later authors, after the long mediaeval night. Wilhelm Griesinger, one of the most important founders of German scientific psychiatry, also described (1845) the change from melancholia to mania, which, in his opinion, is ‘usual’. He believed that the disease is ‘a circle of both types with regular changes’. Griesinger further described ‘seasonal affective disorders’: melancholia usually has its beginning in autumn and winter, mania in spring. He finally described rapid cycling types of affective disorders. Karl Kahlbaum, in introducing Falret’s term ‘folie circulaire’ into German-speaking psychiatry (1863), wrote that the observations and opinions of Griesinger (1845) were decisive for the development of the concept of the French school.

Haustgen (1995) mentioned in his history of bipolar disorders that in the 17th and 18th century Willis (1676), Morgagni (1761) and Lorry (1765) described the recurrent longitudinal association of mania and melancholia. As Stone (1979) observes, the development of scientific inquiry in the 18th century brought significant progress in the understanding of mental disorders: in England, Richard Mead (1673–1754) suspected that mania and melancholia were different aspects of the same process (like Aretaeus of Cappadocia). Vincenzo Chiarugi (1759–1820), in Tuscany, developed a taxonomy based on melancholia, mania and amentia (imbecility) and wrote: “Mania signifies raving madness. The maniac is like a tiger or a lion, and in this respect mania may be considered as a state opposite to true melancholia” (Aretaeus had expressed himself similarly ~2000 years earlier). In the 19th century French psychiatry rose to preeminence as a consequence of its careful descriptive psychopathology (Pichot, 1995). Pinel (1801) and Esquirol (1838) still adhered to the traditional concept that manic and melancholic episodes were separate syndromes of mental illness.

4. The ‘birth’ of the modern concept of bipolar disorder

Nevertheless, neither the ancient physicians nor the psychiatrists of the 19th century mentioned above drew the conclusion that bipolar disease is an entity of its own. This conclusion was drawn for the first time in France in the middle of the 19th century at the hospital La Salpêtrière in Paris by a pupil of Esquirol, Jean-Pierre Falret. In 1851 Falret published a 14-sentence-long statement in the *Gazette des Hôpitaux* (‘De la folie circulaire ou forme de maladie mentale caractérisée par l’alternative régulière de la manie et de la mélancholie’). In this statement Falret described for the first time a separate entity of mental disorder which he named ‘folie circulaire’, characterized by a continuous cycle of depression, mania and free intervals of varying length. Jean-Pierre Falret completed his concept in the following 3 years, and published it in 1854 (Falret, 1854) in the ‘Leçons cliniques de médecine mentale faites à l’hospice de la Salpêtrière’. Some

weeks later he presented it in the Académie de la Médecine under the title ‘Mémoire sur la folie circulaire, forme de maladie mentale caractérisée par la reproduction successive et régulière de l’état maniaque, de l’état mélancholique, et d’un intervalle lucide plus ou moins prolongé’. He defined the sequential change from mania to melancholia and vice versa and the interval in between as an independent disease of its own, namely the ‘folie circulaire’ (Angst, 1997a; Langer, 1994; Marneros, 1999; Pichot, 1995).

Three years after Falret’s first publication Jules Baillarger presented in 1854 his concept of ‘folie à double forme’, both in protocols of a meeting of the Académie de la Médecine and in his paper ‘De la folie à double forme’ (arguing aggressively against Falret). Indeed, the conclusions drawn by the two very different, hostile ‘fathers’ of the concept of bipolar disorders vary considerably: Baillarger 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 interval between the manic and the melancholic episode in his concept; even episodes of mania and melancholia separated by a long interval belong together, forming the ‘folie circulaire’.

The real progress from the views of Aretaeus of Cappadocia, of Richard Mead, Vincenzo Chiarugi or Esquirol was Jean-Pierre Falret’s concept of ‘folie circulaire’; Jules Baillarger’s concept of ‘folie à double forme’ was very similar to the views of his teacher Esquirol (Angst, 1997a; Pichot, 1995). The concepts of ‘folie circulaire’ and ‘folie à double forme’ found widespread distribution in France, and very soon also in other European nations, especially in the German-speaking countries. In 1863 Karl Kahlbaum introduced both terms into German psychiatry in his important book: ‘The Grouping and Classification of Mental Disorders’. Kahlbaum supported Falret and opposed Baillarger. In the same book Kahlbaum pointed out that the observations and opinions of Griesinger (1845), as mentioned above, were of fundamental importance for Falret’s concept. With his paper ‘Über cyclisches Irresein’ (‘On Circular Insanity’; Kahlbaum, 1882) and in ‘Katatonia’ (Kahlbaum, 1884) Kahlbaum contributed to its final establishment.

The concept of ‘folie circulaire’ found not only

enthusiastic supporters, but also critical opponents such as Ludwig Meyer (1874), who labelled it ‘meaningless’. But 10 years later Kahlbaum (1884) presumed that the concept of ‘circuläres Irresein’ (‘circular insanity’) had finally found general acceptance; this acceptance was demonstrated in other countries by publications in ‘Brain’ (Foville, 1882), and in the *American Journal of Insanity* (Hurd, 1884; Angst, 1997a; Langer, 1994; Marneros, 1999; Pichot, 1995).

5. Emil Kraepelin: unification and regression

The work of Emil Kraepelin is so fundamental that to label him the ‘father of modern psychiatry’ is absolutely justified. The dichotomy of ‘endogenous’ psychoses into ‘dementia praecox’ and ‘manic-depressive insanity’ (Kraepelin, 1893, 1896) was of critical importance for the development of psychiatry, in spite of some weaknesses (of which Kraepelin himself was aware). In particular his contribution to the understanding, diagnosis and prognosis of manic-depressive illness was enormous. However, the elimination of the distinction between depressive and circular forms, and the inclusion of all types of affective disorders in the unitary concept of manic-depressive illness, proved later to be a step back (Angst, 1997a; Marneros, 1999). But it was not Kraepelin himself who was dogmatic, but his epigones (Angst, 1999). Kraepelin himself had serious doubts. He expressed his unanswered questions and he was always seeking solutions, as he demonstrated in his last important work in 1920, ‘Die Erscheinungsformen des Irreseins’ (‘The Phenomenological Forms of Insanity’). The unification of ‘circuläres Irresein’ (‘circular insanity’) with depressive types into ‘manisch-depressives Irresein’ (‘manic-depressive insanity’) was carried out in two fundamental publications in 1899: the first of them was ‘Die klinische Stellung der Melancholie’ (‘The Clinical Position of Melancholia’), published in the ‘*Monatsschrift für Psychiatrie und Neurologie*’ (Kraepelin, 1899a), and the second was the sixth edition of his handbook (Kraepelin, 1899b). This unification was a new conclusion of Kraepelin, which contradicts former opinions. In earlier editions of his handbook (Kraepelin, 1883, 1887), Kraepelin

described Falret’s concept of ‘folie circulaire’ as ‘a very well established type of mental disorder’. The first roots of the unification and development of the concept of ‘manic-depressive insanity’ originated at the beginning of the 1890s. In the edition of 1893 the concept is already clear and in 1899 complete. He wrote in ‘The Clinical Position of Melancholia’:

“Unfortunately our textbooks not help us at all in distinguishing between circular depression and mania in cases where the course itself is not informative. The description of melancholic states is absolutely identical with 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.” (Kraepelin, 1899a, p. 328).

And some pages later:

“Apart from our experience that in a whole series of manic episodes a depressive one can occur unexpectedly, and 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 episode 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.” (Kraepelin, 1899a, p. 333).

Contrary to current opinion, Kraepelin himself was not rigid concerning his taxonomies or concepts. The opposite is true; he was open to persuasion by data-orientated research, even by his own fellows, and he often revised his concepts. Doubts and remaining questions regarding his taxonomies and concepts were not a taboo, but were discussed in his publications, such as his last very important publication of 1920 cited above. His epigones, however, lacking his flexibility, ignored the important contributions of Wernicke, Kleist, Leonhard and others. The consequence was nosologic stagnation for al-

most 70 years with regard to new developments in the field of bipolar disorders (Angst, 1999; Marneros, 1999).

6. The opposition to Kraepelin

In opposition to Kraepelin's view in Scandinavia 'depressio mentis periodica' remained a separate affective disorder in the work of Lange (1896), Christiansen (1919) and Pedersen et al. (1948). Benon (1926) proposed separating periodic depression from manic-depressive disorder but met with little approval.

Kraepelin's unification of all affective disorders within the concept of manic-depressive illness also caused strong opposition in Germany, especially under the leadership of Carl Wernicke and later also his colleague in Halle, Karl Kleist. Wernicke differentiated very subtly the different kinds of affective syndromes. For example, he distinguished five different types of melancholia: affective melancholia, depressive melancholia, melancholia agitata, melancholia attonita and melancholia hypochondriaca (Wernicke, 1900, 1906). He challenged Kraepelin's opinion that melancholia is only a part of the manic-depressive illness. In Wernicke's opinion manic-depressive illness should only be understood as described by Falret (folie circulaire) or by Baillarger (folie à double forme). Single episodes of mania or melancholia respectively, recurrent depression or recurrent mania without changing into one another are something different from manic-depressive insanity (Wernicke, 1900). The opinion of Wernicke was the basis for the work of his fellows, such as Kleist, Neele and Leonhard (Angst, 1997a, 1999; Marneros, 1999; Pillmann et al., 2000).

Karl Kleist (a colleague of Wernicke in Halle and later head of the university hospitals in Rostock and Frankfurt) opposed Kraepelin's concept of manic-depressive insanity. Kleist differentiated between unipolar ('einpölig') and bipolar ('zweipölig') affective disorders (Kleist, 1911, 1926, 1928, 1953). The concepts of Wernicke and Kleist were completed by Karl Leonhard (a colleague of Kleist and later head of the Charité in Berlin), who classified the 'phasic psychoses' into 'pure phasic psychoses' (such as 'pure melancholia', 'pure mania', etc.) and 'poly-

morphous phasic disorders' ('vielgestaltige phasische Psychosen'). To the last-mentioned category belong manic-depressive illness and the cycloid psychoses (Leonhard, 1957, 1995). Neither Kleist nor Leonhard considered monopolar mania to be a component of bipolar disorders in present-day terms. On the contrary, they described monopolar mania separately from manic-depressive disorders (Leonhard, 1957). This does not detract from the great significance of their role in stimulating research and paving the way for further development (Angst, 1997a; Marneros, 1999).

The classification of Wernicke, Kleist and Leonhard was nevertheless very complicated, with its multiple subgroups and distinctions, and did not find broad acceptance. Unfortunately, one of the most important aspects of their system, namely the unipolar/bipolar distinction, remained largely unrecognized by international psychiatry.

7. The 'rebirth' of bipolar disorder

The rebirth of bipolar disorders occurred in 1966 with two important publications. The first was the monograph of Jules Angst in Switzerland: 'Zur Ätiologie und Nosologie Endogener Depressiver Psychosen' ('On the Aetiology and Nosology of Endogenous Depressive Psychoses'). The second was published some months later in a supplement of *Acta Psychiatrica Scandinavica* by Carlo Perris (partly in cooperation with d'Elia) with the title: 'A Study of Bipolar (Manic-Depressive) and Unipolar Recurrent Depressive Psychoses' (Perris, 1966). Both publications supported, independently of one another, the nosological differentiation between unipolar and bipolar disorders. Thus, 67 years after Kraepelin's creation of 'manic-depressive insanity' and some 150 years after Falret's and Baillarger's statements, the concept of bipolar disorders experienced a 'rebirth' (Pichot, 1995). Due to the work of Angst and Perris, as well as that of Winokur et al. (1969), who published similar findings in a monograph 3 years later in the USA (Winokur and Clayton, 1967), not only Falret's and Baillarger's concepts have been replicated, completed and developed, but also essential aspects of the work of Wernicke (1900, 1906), Kleist (1928), Leonhard

(1934, 1937, 1957), Neele (1949) and others. Therefore, the year 1966 can be seen as the ‘year of rebirth of bipolar disorders’ (Marneros et al., 1991; Marneros, 1999; Pichot, 1995).

The study of Jules Angst was based on investigations on 326 patients, treated between 1959 and 1963 at the University Hospital of Zurich (Burghölzli). The four most important conclusions of this study were:

1. Genetic and environmental factors have a synergic impact on the aetiology of endogenous depression.
2. Gender plays an important role in the aetiology of endogenous depression. There is a relationship between female gender and endogenous depression, but bipolar disorders are equally represented in males and females.
3. Manic-depressive illness is nosologically not homogeneous. Unipolar depression differs significantly from bipolar disorders in many characteristics such as genetics, gender, course and premorbid personality.
4. Late-onset depression (Kraepelin’s ‘Involution-smelancholie’) seems to belong to unipolar depression and has only a weak relationship to bipolar disorders.

The study of Perris was carried out between 1963 and 1966 in Sidsjon Mental Hospital, Sundsfall, Sweden on 280 patients. Perris’ findings were very similar to those of Angst (Angst and Perris, 1968). They showed also that ‘unipolar mania’ is genetically very strongly related to bipolar disorders, so that clinical and genetic factors support the assumption that the separation of the group of unipolar mania is an artefact.

8. Cyclothymia

Cyclothymia also belongs to the group of bipolar disorders. ‘Cyclothymia’ is an old and controversial term (Brieger and Marneros, 1997a,b,c; Marneros, 1999), first published by Hecker (1877), but coined by his teacher and brother-in-law Kahlbaum. He described with the term (‘Cyklothymie’) periodic changes of depression and ‘exaltation’. Kahlbaum

grouped cyclothymia together with dysthymia and hyperthymia as ‘partial mental disorder’ (‘partielle Seelenstörungen’) with ‘non-degenerative outcome’. By ‘cyclothymia’ Kahlbaum meant the mildest type of bipolar disorder, a definition which was accepted also by Hecker (1898) and by Kraepelin (1899b), together with other authors at the beginning of the 20th century. Jelliffe (1911) imported the opinions of Hecker, Kahlbaum, Falret and Kraepelin to the American psychiatric literature with his work ‘Cyclothymia — The Mild Forms of Manic-Depressive Psychoses and the Manic-Depressive Constitution’. Ernst Kretschmer and Kurt Schneider contributed to a dichotomy of the term ‘cyclothymia’. Kretschmer, in his fundamental work ‘Body Constitution and Character’ (‘Körperbau und Charakter’) (1921–1950), described the ‘cyclothymic average man’ and the cycloid temperaments. Cyclothymia is, in his opinion, “a broad constitutional overterm involving health and disease in the same way”. In contrast, Schneider (1950–1992) accepted this term only for diseases, and he used it synonymously with manic-depressive illness. His influence is still extant in Germany, so that two meanings of cyclothymia persist: manic-depressive illness (increasingly rare) and cyclothymia according to ICD-10 and DSM-IV (increasingly common). The boundaries of cyclothymia as a disorder of the bipolar spectrum or as a disorder of temperament or personality are not fully established (Akiskal et al., 1977, 1979, 1995; Akiskal, 1994, 1996). Thus it is not absolutely clear whether a labile-cyclothymic temperament can be clinically distinguished from bipolar II (Akiskal et al., 1995; Marneros, 1999).

9. Hypomania

Hypomania was described, conceptualized and named by Erich Mendel in 1881 in his book ‘Die Manie’ (oriented on Hippocrates, the first to use the term ‘hypomaenomenoi’, i.e. ‘hypomanics’) to characterize a type of hyperthymic personality.

Mendel wrote: “I recommend (taking under consideration the word used by Hippocrates ‘u(p)omai(n)o/menoi’) the types of mania, having a lower intensity of its phenomenological picture, to name them hypomania” (Mendel, 1881, p. 109).

C.G. Jung, in an early publication (Jung, 1904), recorded in detail a number of cases of manic mood changes ('manische Verstimmung') in patients characterized by a stable submanic complex of symptoms, which had mostly developed in youth and lasted many years without remission. Jung found that exacerbations could occur in the course of the disorder and saw social restlessness and social problems, alcoholism, delinquency, and what he termed 'moral insanity', characterizing these patients as submanic symptoms. The symptoms described by Jung would correspond to today's hyperthymia or very mild mania. Hypomania won more relevance in the last few decades due to the descriptions of bipolar II disorders (Dunner et al., 1976), recurrent brief hypomania (Angst, 1997b) and its relationship with hyperthymic temperament (Akiskal, 1992; Akiskal and Akiskal, 1992).

10. Expanding the group of bipolar disorders

After experiences in pharmacotherapy and prophylaxis of unipolar and bipolar disorders, intensive research on this topic began. One of the many important consequences was the 'expansion' of the group of bipolar and unipolar disorders, as well as the knowledge that they are not homogeneous (Marneros, 1999b). The most important expansions concern the following points:

1. The distinction of schizoaffective disorders into unipolar and bipolar as well as mixed types
2. The renaissance of Kraepelin's mixed states
3. The renaissance of Kahlbaum's and Hecker's concept of cyclothymia and other bipolar spectrum disorders

10.1. Schizoaffective disorders

Karl Kahlbaum can be considered the first psychiatrist in modern times to describe schizoaffective disorders as a separate group in 'vesania typica circularis' (Kahlbaum, 1863). For this definition Kahlbaum applied cross-sectional and longitudinal aspects. Emil Kraepelin was also acquainted with cases between 'dementia praecox' and 'manic-depressive insanity' (Kraepelin, 1893, 1896, 1920). These

'cases-in-between' were a problem for him, a nuisance, but on the other hand an interesting conundrum to be solved. As is well known, Kraepelin dichotomized the so-called endogenous psychoses into two groups, namely 'dementia praecox' (with a poor outcome) and the 'manic-depressive insanity' (with a favourable outcome). But he already knew that not all cases of endogenous mental disorders can readily be classified into the two categories. Some cases of mixed states, delirious mania and other mental disorders described by Kraepelin (1893, 1920) could be allocated to either category or to neither of them. In a critical appraisal of his own taxonomy, Kraepelin wrote in his important paper of 1920, 'Die Erscheinungsformen des Irreseins' ('The Phenomenological Forms of Insanity'), that mental disorders can have elements of both groups of mental disorders, namely 'dementia praecox' and 'manic-depressive insanity' and they also can have a different course and a different prognosis than 'dementia praecox'. He knew that the boundaries between the two groups of mental disorders are elastic and that there are bridges connecting them. His doubts became stronger in the wake of an investigation by his pupil and colleague Zendig. Zendig reported in his paper 'Contributions to Differential Diagnosis of Manic-Depressive Insanity and Dementia Praecox' (Zendig, 1909) that ~30% of Kraepelin's sample diagnosed with 'dementia praecox' (using Kraepelin's guidelines) had a course and outcome not corresponding to that of 'dementia praecox'; Zendig attributed the good outcome to an incorrect diagnosis. Later Kraepelin saw in such cases a weakness of his dichotomy concept. He wrote: "The cases which are not classifiable (namely to manic-depressive insanity or dementia praecox) are unfortunately very frequent" (Kraepelin, 1920, p. 26). Two pages later he made a decisive and for him certainly not an easy statement: "We have to live with the fact that the criteria applied by us are not sufficient to differentiate reliably in all cases between schizophrenia and manic-depressive insanity. And there are also many overlaps in this area" (i.e. between schizophrenia and affective disorders; Kraepelin, 1920, p. 28).

As early as 1966, Jules Angst investigated the schizoaffective disorders, under the term 'Mischpsychosen' ('mixed psychoses'), as a part of the

affective disorders (Angst, 1966). This was an outlier's position, not only against the 'Zeitgeist', but also contrary to the opinion of his teacher Manfred Bleuler, who assumed them to be a part of schizophrenia. Later investigations by Angst et al. (1979, 1989, 1990), by Clayton et al. (1968), by other members of the Winokur group (Fowler et al., 1972), by Cadoret et al. (1974) and the comparative studies of Marneros et al. (1986a,b,c, 1988a,b,c, 1989a,b,c, 1991) supported more and more the opinion that the relationship between schizoaffective and affective disorders is stronger than that between schizoaffective and schizophrenic disorders.

Studies in the last three decades (Angst, 1989; Marneros, 1999; Marneros et al., 1989a,b,c, 1990a,b,c, 1991) have yielded evidence as follows:

1. Schizoaffective disorders should be separated into unipolar and bipolar disorders, like affective disorders.
2. Bipolar schizoaffective disorders have a stronger relationship to bipolar affective disorders than either group has to unipolar schizoaffective disorders.

Marneros and co-workers proposed that bipolar schizoaffective disorders belong together with bipolar affective disorders, and unipolar schizoaffective together with unipolar affective disorders, in two voluminous groups (Marneros et al., 1990a,b,c, 1991; Marneros, 1999).

10.2. Mixed states

In recent years there has been renewed interest in mixed states or mixed bipolar disorders, especially in the USA (Himmelhoch et al., 1976; Post et al., 1989; Akiskal, 1992a,b, 1996; McElroy et al., 1992; Bauer et al., 1994b), but also in Italy (the Pisa group, Perugi et al., 1997), in France (the EPIMAN study, Akiskal et al., 1998), and in Germany (Marneros et al., 1991, 1996a,b, Marneros, 1999). Although the creator of the concept is doubtless Emil Kraepelin, with the assistance of his co-worker Wilhelm Weygandt (Weygandt, 1899; Marneros, 1999, 2001), such disorders were observed and described much earlier. The first descriptions of mental disorders which could be characterised as 'mixed states' are

rooted in the work of the Greek physicians of classical times, especially Hippocrates (460–337 BC) and Aretaeus of Cappadocia (1st century AD). In 1852, Pohl, in Prague, described in a large monograph on melancholia mixed states occurring during the transition from melancholia to mania (Pohl, 1852, pp. 121, 127), 'poriomanic' melancholia (p. 186) and marked anxiety states as transitional phenomena of depression (pp. 111–121). He also described rapid cycling between melancholia and brief mania (p. 111), later described as a more regular alternation of cyclicity by Focke (1862), as lasting 3–4 weeks by Jules Falret (1879), pp. 58, 66) or just a few (6) days by Kelp (1862).

Kraepelin used the term 'Mischzustände' ('mixed states') resp. 'Mischformen' ('mixed forms') for the first time in the fifth edition of his textbook (Kraepelin, 1896, p. 634) and conceptualized them definitively in the sixth edition (Kraepelin, 1899b). Kraepelin, as well as his pupil Wilhelm Weygandt, described in 1899 six types of mixed states (Weygandt, 1899):

1. Depressive or anxious mania ('depressive oder ängstliche Manie')
2. Excited or agitated depression ('agitierte Depression')
3. Mania with thought poverty ('ideenarme Manie')
4. Manic stupor ('manischer Stupor')
5. Depression with flight of ideas ('ideenflüchtige Depression')
6. Inhibited mania ('gehemmte Manie')

Kraepelin further distinguished two groups of mixed states:

1. 'Transition forms' — a stage-in-between, when depression changes into mania or vice versa
2. 'Autonomic forms' — a disorder of its own

An interesting enrichment — really the first new conceptual aspect since 1899 — was contributed by Akiskal, based on Kraepelin's 'mixed concept' (Akiskal, 1992a,b, 1996; Akiskal and Mallya, 1987). Kraepelin suggested a mixing of manic or depressive symptoms with cyclothymic, hyperthymic or depressive temperament. The mixing of symptoms and

temperament created in Akiskal's view, three different types of mixed states:

- Depressive temperament + manic psychosis
- Cyclothymic temperament + depression
- Hyperthymic temperament + depression

It is noteworthy that in the scheme of Akiskal (1992b), mixed states (at least the first and last types) arise when an episode arises from a temperament of opposite polarity. Partial support for the foregoing schema has derived from collaborative research conducted in Italy and France (Dell'Osso et al., 1991, 1993; Perugi et al., 1997; Akiskal et al., 1998). There is also increasing support for the idea that subthreshold admixtures of depression with mania — or hypomanic intrusions into major depression — represent sufficient grounds for the diagnosis of mixed states (Akiskal and Mallya, 1987; Bauer et al., 1994b; McElroy et al., 1995; Perugi et al., 1997; Akiskal et al., 1998).

In the last two decades has also been described a 'mixed type of schizoaffective disorders', which is a combination of mixed bipolar affective disorders and schizophrenic symptoms (Marneros et al., 1986a,b,c, 1988a,b,c, 1991, 1996a,b). The mixed type of schizoaffective disorder is analogous to the mixed type of affective disorders (Marneros, 1999).

11. Bipolar spectrum

The concept of a continuum of manic conditions developed by Kretschmer (1921–1950) and Eugen Bleuler (1922) has undergone various modern attempts at elaboration into subtypes (Angst, 1997a; Marneros, 1999). Klerman (1981) distinguished six subtypes of bipolar disorders: mania, hypomania, hypomania or mania precipitated by drugs, cyclothymic personality, depression with a family history of bipolar disorder, and mania without depression. Dunner et al. (1976) distinguished depressions with hypomania (bipolar II) from those with mania (bipolar I). Angst (1978) based his approach on a continuum distinguishing between hypomania (m), cyclothymia (md), mania (M), mania with mild depression (Md), mania and major depression (MD), and major depression and hypomania (Dm). More

recently, brief hypomania, lying under the threshold of DSM-IV hypomania, with a duration of as little as 1–3 days, has been described, and there is also some evidence for a valid subcategory of recurrent brief hypomania (Angst, 1990, 1997a,b,c; Angst et al., 1990; Angst and Merikangas, 1997).

Over the past 20 years Akiskal has provided evidence, based on good clinical observation and sound knowledge of the classical literature, for the desirability of enlarging the continuum to encompass several diagnostic subgroups, including what he terms the 'soft' bipolar spectrum (Akiskal, 1983a, 1996; Akiskal and Mallya, 1987; Akiskal and Pinto, 1999). A new concept includes 'pseudo-unipolar disorders', defined as recurrent depressions without spontaneous hypomania but often with bipolar family history; alternatively considered bipolar III, this category refers to recurrent depression switching to hypomania under antidepressant treatment. Bipolar IV describes major depressions superimposed on hyperthymic temperament. Akiskal and Pinto (1999), to emphasize the concept of a continuum within this broad spectrum, have actually made provision for intermediary forms, such as bipolar $I\frac{1}{2}$ (protracted hypomania), bipolar $II\frac{1}{2}$ (cyclothymic temperament + major depression), and bipolar $III\frac{1}{2}$ (major depression + stimulant abuse).

There are several problems with the concept of a bipolar spectrum. One is that hypomanic symptoms in 'drug-induced hypomania' have not been the object of systematic assessment in clinical trials of antidepressants and there is no proof coming from placebo-controlled studies. However, prospective follow-up studies indicate that depressions with hypomania first manifested on antidepressants, often progresses to bipolar disorder (Akiskal et al., 1979, 1983a,b; Strober and Carlson, 1982). The more serious problem with the concept of a bipolar spectrum is that family studies do not fully support it (Coryell, 1999). Thus, as proposed by Akiskal (1996), the spectrum concept refers to a clinical rather than a genetic spectrum.

Although somewhat controversial, there is emerging consensus that a rapid-cycling course, often associated with excessive antidepressant use, belongs to the realm of broadly conceived bipolar disorders (Koukopoulos et al., 1980; Wehr and Goodwin, 1987; Coryell et al., 1992; Bauer et al., 1994a).

There is good evidence supporting Kraepelin's assumption that subjects with 'manic-type' (hyperthymic) temperaments belong to the bipolar spectrum (Akiskal, 1992a; von Zerssen et al., 1996). In addition, certain subtypes of personality disorders ('histrionic-sociopathic' or 'borderline-narcissistic') may also belong to cyclothymic temperaments (Akiskal et al., 1977; Akiskal, 1981, 1994; Akiskal et al., 1985). The borderline concept propounded by Kernberg (1967, 1975) has given further impetus to research into bipolar disorder in the work of Stone (1979, 1980) who, through careful family study, showed borderline disorder to be closer to manic-depressive disorder than to the schizophrenic spectrum. The affiliation to manic-depressive disorder would also explain the high suicidality in borderline states. But there are difficulties in identifying this subtype of borderline personality as indicated by Gunderson and Phillips (1991): boundaries between borderline disorders and recurrent and labile mood

disorders (Akiskal et al., 1985) needed further clarification. The modern concept of a bipolar spectrum would embrace all these conditions and include the hyperthymic and cyclothymic temperaments (Akiskal, 1983a, 1996). Marneros (1999) further suggested a continuum between normal fluctuations of an 'adjustable homeostasis' of affectivity all the way up to highly psychotic disorders (Fig. 1).

A proposal for a psychotic continuum was obviously supported by operational data (see also contributions in Marneros et al., 1995).

12. Future work

Research into the subgroups of bipolar disorders is undoubtedly still in its infancy. Most studies have so far been restricted to mania and have reported, for instance, low lifetime prevalence of bipolar disorder (0.2–1.6%; Picinelli and Gomez Homen, 1997). The

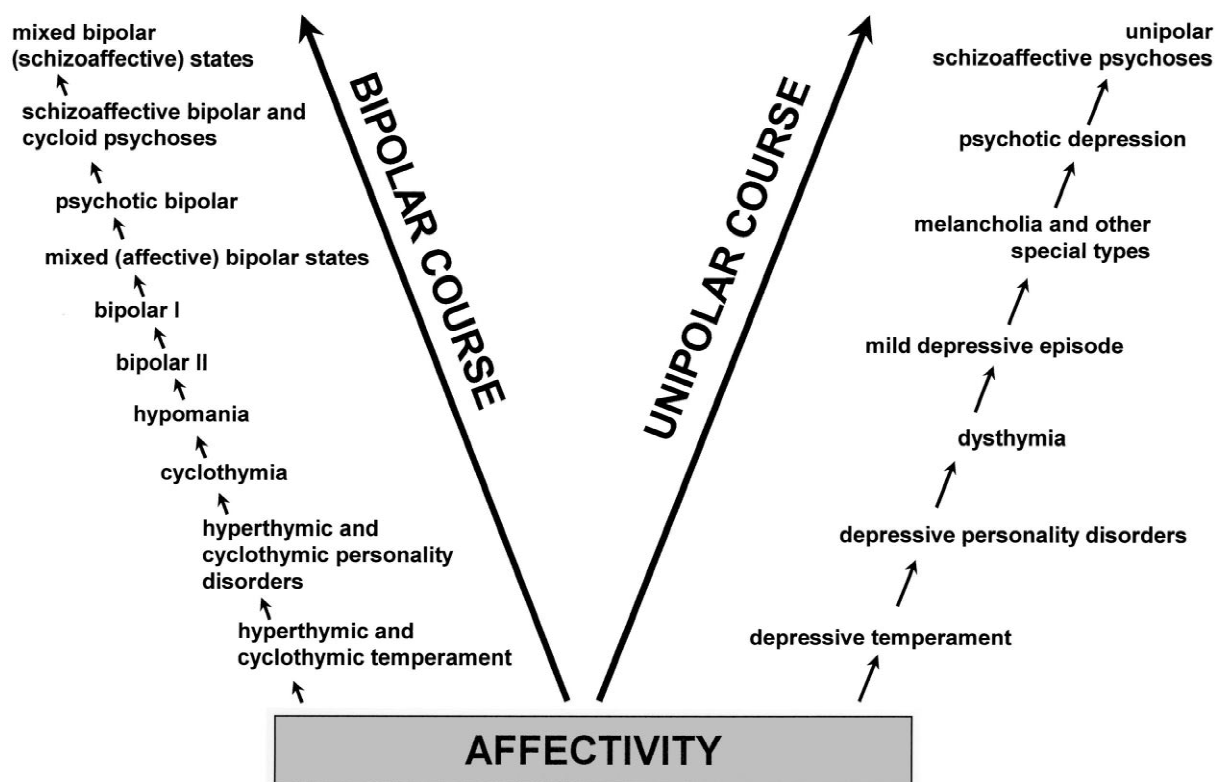


Fig. 1. Bipolar and unipolar continuum (Marneros, 1999).

inclusion of hypomania, brief hypomania and cyclothymic disorders raises the rates to 3–7% (Angst, 1995a,b, 1998) and underlines the significance of the ‘soft bipolar spectrum’ (Akiskal and Mallya, 1987). Further studies are needed in order to distinguish clearly between hyperthymic and cyclothymic temperaments on the one hand and recurrent brief hypomania or recurrent brief cyclothymia on the other. The same is true for the subgroups M, Md, MD, DM, md, m (Angst, 1978), a classification that moves beyond the dichotomy between bipolar I and bipolar II disorders. In 1976 Dunner and co-workers distinguished bipolar II from bipolar I disease. The essential feature of bipolar I disorder is a clinical course characterized by the occurrence of one or more manic episodes or mixed episodes (Dunner et al., 1976; APA, 1994). The essential feature of bipolar II disorders is a clinical course characterized by the occurrence of one or more major depressive episodes, accompanied by at least one hypomanic episode. It is probable, in fact, that there is no clear delineation among all the subtypes, which may be artificially constructed on a natural continuum from transient to persistent hypomanic and manic manifestations of varied length, frequency and severity. It is this spectrum concept that currently attracts the most interest (Akiskal and Pinto, 1999). A recent monograph, edited by Akiskal (1999), goes into great depth in describing contemporary concepts of ‘bipolarity beyond classic mania’.

But also the group of schizoaffective disorders have to be investigated from the point of view of bipolarity, as well as of the sequential changes of the type of episodes. There is good evidence that on a longitudinal axis cases with change between schizophrenic and affective episodes belong also to the schizoaffective spectrum (Marneros et al., 1986a,b,c, 1991; Marneros, 1999). The ‘schizobipolar’ group might be reclassified in the schema of Akiskal and Pinto (1999) as a bipolar type $\frac{1}{2}$ (i.e. the more severely psychotic edge of bipolar I). The perspective of Akiskal and Pinto (1999) would cohere with the bipolar branch of Fig. 1 (Marneros, 1999). These considerations would also generally cohere with the framework of Gershon et al. (1982) who, in systematic family studies, have demonstrated within bipolar pedigrees, the entire spectrum of schizoaffective, bipolar I, bipolar II and certain ‘unipolar’ cases.

Such a broad spectrum concept of bipolarity — contemporaneously reborn in the clinical work of Akiskal (1983a) and the epidemiologic research of Angst (1998) — has received endorsement in the classic modern monograph of Goodwin and Jamison (1990).

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