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# Bipolar disorders beyond major depression and euphoric mania

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## Introduction: knowledge from the past, goals for the future

The last five decades have brought essential changes and developments in psychiatry. One of the most important reasons for these developments is certainly the psychopharmacological revolution. The discovery of antipsychotics, antidepressants, mood stabilizers, and other psychotropic substances has had an enormous impact, not only on many fields of research, treatment, social life, and social politics, but also on ideological aspects and attitudes. Concerning psychiatric research, the psychopharmacological revolution has been an important and sustained stimulus not only for the development of neuroscience, genetics, and pharmacology, but also for psychiatric methodology, the development of new diagnostic concepts, and new research on treatment, prognosis, and rehabilitation. One indirect but fundamental development was the rediscovery and rebirth of old diagnostic, nosological, and phenomenological concepts. For example, new pharmacological experiences led to the rediscovery of the relevance of the unipolar–bipolar dichotomy. The concepts examined by Falret (1854), Baillarger (1854), Kleist (1929, 1953), Neele (1949), Leonhard (1957), and others were confirmed in the new psychopharmacological era, including the nosological refinements made by Jules Angst (1966), Carlo Perris (1966), Winokur and Clayton (1967), and others. But soon the enthusiasm for the new psychopharmacology gave way to an increasing awareness of some limitations. Within broadly defined diagnostic groups like schizophrenia, depression, and bipolar disorder, many patients proved to be non-responders or partial responders. The identification of such non-responder groups and their careful investigation showed some special or atypical features, like coexistence of manic and depressive symptoms or schizophrenic and mood symptoms (depressive and manic), as well as rapid changes of mood states or rapid onset of episodes. As a result, the

old concepts of mixed states, schizoaffective disorders, rapid cycling, cyclothymia, atypical depression, and others underwent a rebirth (Goodwin and Jamison, 1990; Marneros, 1999, 2001; Marneros and Angst, 2000; Angst and Marneros, 2001). But some of the rediscovered psychopathological states – although very well described – are still *terra incognita* and a source of confusion for many psychiatrists. Thus, more educational efforts are needed. This book summarizes our current knowledge on these atypical forms, and makes suggestions for much needed additional research.

## Mixed states

### The ancient times

The early descriptions and roots of mixed states are very closely connected with the history and development of concepts regarding bipolar disorders. These concepts have their roots in the work and theories of the Greek physicians of the classical period, especially of the school of Hippocrates and, later, of the school of Aretaeus of Cappadocia (Marneros and Angst, 2000; Angst and Marneros, 2001; Marneros, 2001).

Hippocrates based his work partially on the views of Pythagoras and his scholar Alcmeon and partially on the views of Empedocles. Like Alcmeon, Hippocrates (Fig. 1.1) thought that the origin of mental diseases lay in the disturbed interaction of body fluids with the brain. Affective pathological states, as well as psychotic states, are the results of illnesses or disturbances of brain functions. He wrote in *About the Sacred Disease*:

*Εἰδέναι δέ χρή τούς ἀνθρώπους ὅτι ἐξ οὐδενός ἡμῖν αἱ ἡδοναί γίνονται καί εὐφροσύναι καί γέλωτες καί παιδιαί ἢ ἐντεῦθεν, καί λῦπαι καί ἀνίαι καί δυσφροσύναι καί κλαυθμοί. καί τούτῳ φρονέομεν μάλιστα καί βλέπομεν καί ἀκούομεν καί διαγιγνώσκομεν τά τε αἰσχρά καί καλά καί κακά καί ἀγαθά καί ἡδέα καί ἀηδέα, τά μέν νόμῳ διακρίνοντες, τά δέ τῷ συμφέροντι αἰσθανόμενοι, τῷ δέ καί τάς ἡδονάς καί τάς ἀηδίας τοῖσι καιροῖσι διαγιγνώσκοντες οὐ ταῦτα ἀρέσκει ἡμῖν. τῷ δέ αὐτῷ τούτῳ καί μαινόμεθα καί παραφρονέομεν, καί δείματα καί φόβοι παρίστανται ἡμῖν, τά μέν νύκτωρ, τά δέ καί μεθ ἡμέρην, καί ἀγρυπνίαι καί πλάνοι ἄκαιροι, καί φροντίδες οὐχ ἱκνεύμεναι, καί ἀγνωσίαι τῶν καθεστώτων καί ἀηθίαι. καί ταῦτα πά σχωμεν ἀπό τοῦ ἐγκεφάλου πάντα, ὅταν οὗτος μή ὑγιαίνη …*
*People ought to know that the brain is the sole origin of pleasure and joy, 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 fear, 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 things mentioned*

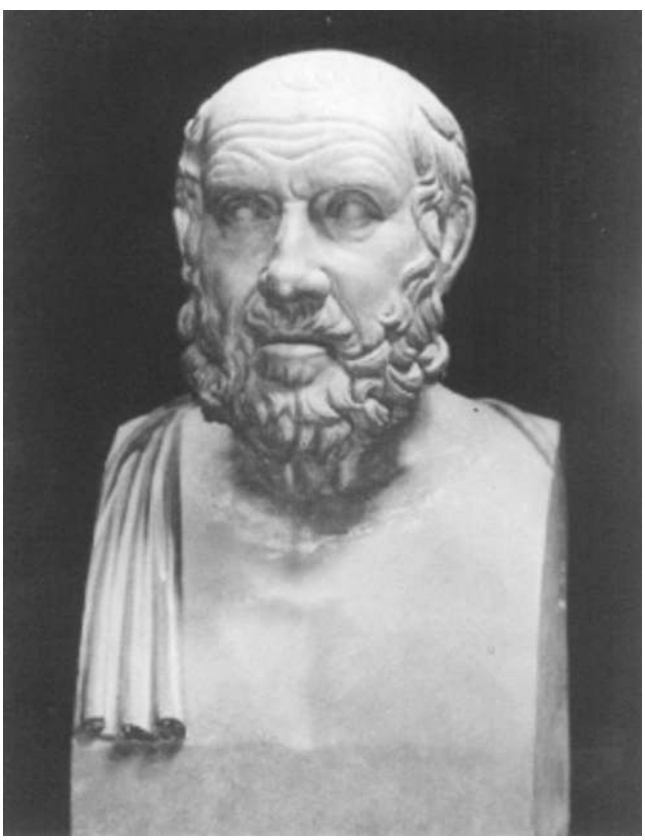


Fig. 1.1 Hippocrates (460–370 BC).

*above through the brain when it is ill* (Hippocrates, 1897: translation of original Greek and German quotations by Andreas Marneros).

Hippocrates also formulated the first classification of mental disorders, namely into melancholia, mania, and paranoia. He also described, together with the so-called Hippocratic physicians, organic and toxic deliria, postpartum psychoses, phobias, personality disorders, and temperaments. They also coined the term "hysteria." The ancient classifications and descriptions of mental disorders provided by Hippocrates and the Hippocratic school present a basis for broader definitions and concepts than the modern ones do. Some authors claimed that the concepts of mania and melancholia as described by Hippocrates (and also by Aretaeus and other Greek physicians) were different from the modern concepts. But this is not correct. The clinical concepts of melancholia and mania were broader than modern concepts – but not different. They included (according to modern criteria): melancholia or mania, mixed states, schizoaffective disorders,


Fig. 1.2 Aretaeus of Cappadocia (AD 81–138).

some types of schizophrenia, and some types of acute organic psychoses and atypical psychoses (Marneros, 1999; Marneros and Angst, 2000; Angst and Marneros, 2001). The similarities but also the differences between the ancient concepts and the modern ones, as well as the involvement of mixed states in these descriptions, can be illustrated by directly quoting the texts written at that time:

Hippocrates assumed long-lasting anxiety, fear (phobos) and moodiness (dysthymia) as basic characteristics of melancholia. He wrote: *"Ην φόβος καί δυσθυμίη πολύν χρόνον διατελέει, μελαγχολικόν τό τοιοῦτον."* *If anxiety (phobos) and moodiness (dysthymia) are present for a longer period, that is melancholia.*

Aretaeus of Cappadocia, one of the most famous Greek physicians, lived in Alexandria in the first century AD (Fig. 1.2). His dates of birth and death are not exactly known (some authors say he lived from around AD 40 to 90, others from AD 50 to 130), but he was a prominent representative of the Eclectics (Marneros

and Angst, 2000) who described a polymorphism of symptoms in melancholia as follows:

*Τεκμήρια μέν οὐν οὐκ ἄσημα· ἤ γάρ ἥσυχοι, ἤ στυγνοί, κατηφέες, νωθροί ἔασι· ἔτι δέ καί ὀργιλοί προσγίγνονται ἀλόγως, οὐ τινί ἐπ᾽ αἴτιη δύσθυμοι, ἄγρυπνοι, ἐκ τῶν ὕπνων ἐκθορυβούμενοι.*
*The symptoms [of melancholia] are not unclear: [the melancholics] are either quiet or dysphoric, sad or apathetic. Additionally, they could be angry without reason and suddenly awake in panic* (van Kappadokien, 1847).

Also, he described a phenomenological polymorphism of mania in Chapter 6 of his first book *On the Causes and Symptoms of Chronic Diseases* as follows:

*Καί οἵσι μέν ἡδονή ἠ μανίη, γελῶσι, παίζουσι, ὀρχεύονται νυκτός καί ἡμέρης, καί ἐς ἀγορήν ἀμφαδόν καί ἐστεμμένοι κοτέ, ὅκως ἐξ ἀγωνίης νικηφόροι, ἐξίασι. ἄλυπος τοῖσι πέλας ἡ ἰδέη. Μετεξέτεροι δέ ὑπό ὀργῆς ἐκμαίνονται … ἰδέαι δέ μύριαι. Τοῖσι μέν γε εὐφύεσι τε καί εὐμαθέσι ἀστρονομίη ἀδίδακτος, φιλοσοφίη αὐτομάτη, ποίησις δῆθεν ἀπό μουσέων.*
*Some patients with mania are cheerful – they laugh, play, dance day and night, and stroll through the market, sometimes with a garland on their head, as if they had won a game: these patients do not worry 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 studied it, with philosophy, but autodidactically, they consider poetry a gift of muses* (van Kappadokien, 1847).

The problem of the polymorphism of mania is also reflected in the writings of the Roman physician Caelius Aurelianus trying to describe the etymology of the word "mania". In his book *On Acute Diseases*. (Chapter 5), Caelius Aurelianus, a member of the Methodist school and student of the Soranus of Ephesos, gave at least six possible etymologies of the word "mania." The fact that he was able to do so demonstrated the many meanings of the term. He wrote:

> The school of Empedocles holds that one form of madness consists of a purification of the soul, and the other of 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 because there is an 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 tough and enduring, Greek *hypomeneticos*" (Caelius Aurelianus, translated by Drabkin, 1950).

The first descriptor of manic-depressive illness as one entity – one disease with two opposite symptomatological constellations – was Aretaeus of Cappadocia (Marneros, 1999, 2001; Angst and Marneros, 2001; Marneros and Angst, 2000). His descriptions of the boundless developments of melancholia into mania led to the thinking that there is not only a "switch" but also a "mixture" of symptoms. In his books: *On the Aetiology and Symptomatology of Chronic Diseases* and *The Treatment of Chronic Diseases*, he wrote: *Δοκέει τέ δέ μοι μανίης γε ἔμμεναι ἀρχή καί μέρος ἡ μελαγχολίη*): "I think that melancholia is the beginning and a part of mania" and: "*οἱ δέ μαίνονται, αὔξῃ τῆς νούσου μᾶλλον, ἢ ἀλλαγῇ πάθεος*": "The development of mania is really a worsening of the disease [melancholia], rather than a change into another disease." And some sentences later: "*Ην δε ἐξ ἀθυμίης ἄλλοτε καί ἄλλοτε διάχυσις γένηται, ἡδονή προσγίγνεται ἐπί τοῖσι πλείστοισι· οἱ δέ μαίνονται*": "In most of them [melancholics], the sadness became better after various lengths of time and changed into happiness; the patients then develop a mania."

Ideas similar to those of Hippocrates and Aretaeus of Cappadocia were also presented by many other 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 Ephesos and his scholar Caelius Aurelianus (who extensively recorded the views of his teacher on phrenitis, mania, and melancholia), and later Galenus of Pergamos. All of these physicians focused their interest on mental disorders, especially melancholia and mania (Alexander and Selesnick, 1966; Fischer-Homberger, 1968).

## From Heinroth to the psychopharmacological revolution

As Koukopoulos and Koukopoulos (1999) pointed out, the nosologists of the eighteenth century, such as Lorry, Boissier de Sauvages, and William Cullen, have already classified among the melancholias such forms as melancholia moria, melancholia saltans, melancholia errabunda, melancholia silvestris, melancholia furens, and melancholia enthusiastica, which are in fact "mixed". But the scientific description really began in the 19th century (Marneros, 2001).

Perhaps the first psychiatrist to systematically describe mixed states was the German professor of psychiatry Johann Christian August Heinroth (1773–1843). He was the first professor of "Mental Medicine" at *a German university (Leipzig)*. In his textbook *Disorders of Mental Life* (1818) he classified mental disorders into three voluminous categories:

The first category comprised the exaltations (hyperthymias). The second category embraced the depressions (asthenias), and the third category, the mixed states of exaltation and weakness (hypo-asthenias) (Heinroth used the

**Table 1.1** Mixture of exaltation and depression according to Heinroth, 1818

| *Hyper-asthenias* |
|---|
| First group: mixed mood disorders (*animi morbi complicati*) |
| 1. *Ecstasis melancholica* |
| 2. *Melancholia moria* |
| 3. *Melancholica furens* |
| 4. *Melancholia mixta catholica* |
| Second group: mixed mental disorders (*morbi mentis mixti*) |
| 1. *Paranoia anoa* |
| 2. *Paranoia anomala* |
| 3. *Paranoia anomala maniaca* |
| 4. *Paranoia anomala catholica* |
| Third group: mixed volition disorders (*morbi voluntatis mixti, athymia*) |
| 1. *Panphobia, melancholia hypochondriaca* |
| 2. *Athymia melancholica* |
| 3. *Athymia paranoica* |
| 4. *Athymia melancholico-maniaca* |

German word "Mischung", which can be translated as "mixture"). This last category of mixed states was divided into mixed mood disorders (*animi morbi complicati*), mixed mental disorders (*morbi mentis mixti*), and mixed volition disorders (*morbi voluntatis mixti*), as shown in Table 1.1. It is evident that mainly in the categories "mixed mood disorders" and "mixed volition disorders," mixed affective and schizoaffective disorders according to modern definitions are involved.

In addition to the above-mentioned mixed states, Heinroth described the pure forms of exaltation (hyperthymias), including *melancholia erotica* and *melancholia metamorphosis*. *Melancholia saltans*, however, is defined by Heinroth as a form of mania (Fig. 1.3).

The French psychiatrist Joseph Guislain described in his book *Treatise on Phrenopathias or New System of Mental Disorders* (1838) a category of mixed states named "joints of diseases." To this category, he allocated "grumpy depression," "grumpy exaltation," and "depression with exaltation and foolishness," which also included "depression with anxiety." The first type, especially, features long episodes and an unfavorable prognosis (Guislain, 1838).

But the real author of what we today call mixed states is Emil Kraepelin (Fig. 1.4). He distilled, conceptualized, and categorized previous knowledge regarding mixed

Fig. 1.3 Johann Christian August Heinroth (1773–1843).

Fig. 1.4 Emil Kraepelin (*c.* 1900).

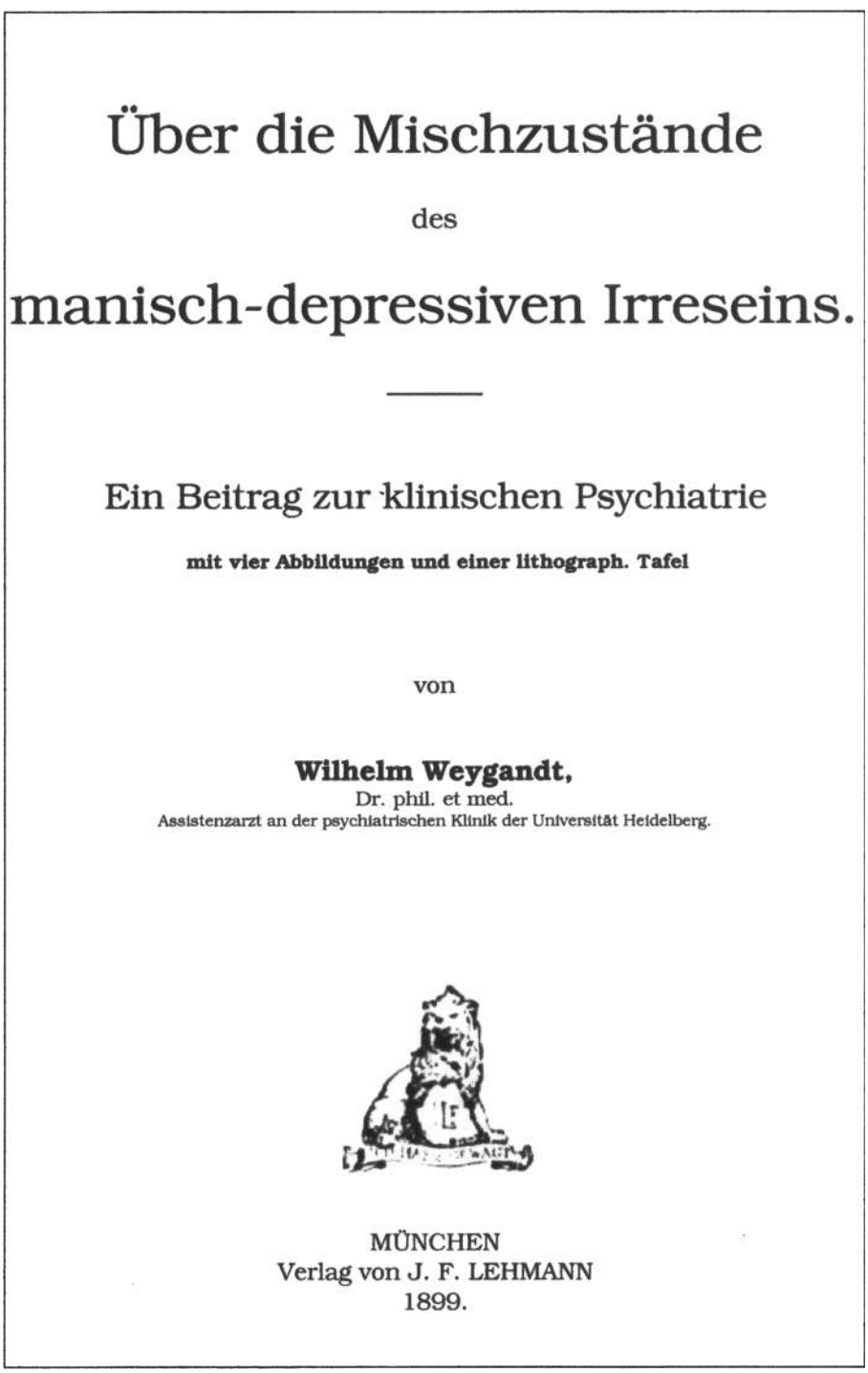
**Table 1.2** The development of Kraepelin's concept of "mixed states"

| 1893 | 1899 | 1904 | 1913 |
|---|---|---|---|
| 1. "Manic stupor" (*manischer Stupor*) | 1. "Manic state with inhibition" (*manische Zustände mit Hemmung*)<br>2. "Depressive states with excitation" (*depressive Zustände mit Erregung*) | 1. "Furious mania" (*zornige Manie*)<br>2. "Depressive excitation" (*depressive Hemmung*)<br>3. "Unproductive mania with thought poverty" (*unproduktive gedankenarme Manie*)<br>4. "Manic stupor" (*manischer Stupor*)<br>5. "Depression with flight of ideas" (*Depression mit Ideenflucht*)<br>6. "Manic inhibition" (*manische Hemmung*) | 1. "Depressive or anxious mania" (*depressive oder ängstliche Manie*)<br>2. "Excited depression" (*erregte Depression*)<br>3. "Mania with thought poverty" (*ideenarme Manie*)<br>4. "Manic stupor" (*manischer Stupor*)<br>5. "Depression with flight of ideas" (*ideenflüchtige Depression*)<br>6. "Inhibited mania" (*gehemmte Manie*) |

states, as well as other mental disorders. Kraepelin used the term *Mischzustände* (mixed states) or *Mischformen* (mixed forms) for the first time in the fifth edition of his textbook (1896, p. 634), although, already in 1893, he had described the "manic stupor" (1 year after Kraepelin's description of manic stupor, Dehio referred to it during the 1894 meeting of "South-western German Alienists"). He practically completed their theoretical conceptualization in the sixth edition (1899, pp. 394–399), although their final categorization and nomenclature came with the eighth edition in 1913 (Table 1.2).

In the same year that Kraepelin's sixth edition (1899) was published, Wilhelm Weygandt (pupil and colleague of Kraepelin in Heidelberg) published the first book on mixed states in psychiatric literature: *Über die Mischzustände des manisch-depressiven Irreseins* (*On the Mixed States of Manic-Depressive Insanity*; see Fig. 1.5).

Since Weygandt referred to the sixth edition of Kraepelin's handbook as a source, it can be assumed that Kraepelin's handbook was published earlier in the year or that Weygandt was familiar with his teacher's manuscript. Kraepelin did



Über die Mischzustände

des

manisch-depressiven Irreseins.

Ein Beitrag zur klinischen Psychiatrie

mit vier Abbildungen und einer lithograph. Tafel

von

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MÜNCHEN
Verlag von J. F. LEHMANN
1899.

Fig. 1.5 The first book in psychiatric literature on mixed states (Weygandt, 1899).