Section 1 Domain Chapters

Chapter 1

Mapping the Terrain of Bipolar II Disorder

Gordon Parker

Any consideration of bipolar II (BP II) disorder requires addressing a number of fundamental issues. Firstly, *does such a bipolar condition exist* – whether differing from bipolar I (BP I) disorder dimensionally or categorically? As detailed earlier (Parker and Paterson, 2017) the concept of hypomania (a key BP II construct) was first defined by Mendel in 1881 – who essentially described a milder version of mania – while, in 1882, Kahlbaum used the term 'cyclothymia' to describe alterations between elation without psychosis and melancholic episodes. During the early twentieth century both cyclothymia and hypomania were lumped together as milder forms of manic depressive psychosis. From the 1930s to the 1970s, the concept of hypomania' or a 'milder form' of bipolar disorder all but disappeared until Dunner identified a putative BP II category in his research studies. Dunner (personal communication) identified a subset of bipolar patients who appeared to be 'in between' those with unipolar depression and those who experienced mania, and who reported less severe 'hypomanic' episodes.

BP II disorder has now been formally categorized for several decades with Shorter (Chapter 2) detailing how it was accorded separate status in the final version of the RDC (Research Diagnostic Criteria) in 1978. In 1980, DSM-III listed an 'Atypical Bipolar Disorder' and positioned it as a 'residual category' (p. 223) for 'individuals with manic features that cannot be classified as Bipolar Disorder or as Cyclothymic Disorder' – exemplified by individuals who have had a previous major depressive episode and who are then presenting with 'some manic features (hypomanic episode) but not of sufficient severity and duration to meet the criteria for a manic episode. Such cases are referred to as "Bipolar II"'. In 1987, DSM-III-R allowed those who had had one or more hypomanic episodes (but 'without Cyclothymia or a history of either a Manic or a Major Depressive Episode') to be listed in a category of 'Bipolar Disorder Not Otherwise Specified'. It achieved formal DSM status (as Bipolar II Disorder) in the 1994 DSM-IV manual, where its essential features were captured by a clinical course of one or more major depressive episodes accompanied by at least one hypomanic episode, albeit with its seven symptom criteria (p. 338) being identical to those defining a manic episode (p. 332). In the 2013 DSM-5 manual Bipolar II Disorder is clearly separated from Bipolar I disorder in the introduction to the relevant chapter. In addition, BP II was formally classified in the 1994 ICD-10 system. Thus, it *exists* as a formalized psychiatric condition and has for an extended period.

It is likely, however, that BP II long existed prior to its formal classification. Davidson (2011) reviewed the mental health 'afflictions' of the first 51 British Prime Ministers, providing evidence suggestive of a BP II disorder in 16% (Canning, Churchill, Disraeli, Grey,

Lloyd George and Macmillan). None received such a diagnosis (as the condition was not then formally classified), and as Davidson details, none lost office as a consequence of their mood swings and with most being judged as superior prime ministers than the others who, if not experiencing depression, were commonly anxious and self-doubting. Most of those with a putative BP II disorder were recognized as having depressive states but their oscillating elevated mood states were either not observed or given differing interpretations, consistent with the longstanding tendency to view those with the condition as simply having mercurial states or a cyclothymic personality style.

Despite its formal categorization for several decades, a diagnostic category may or may not have validity and psychiatry can provide many examples, both historical (e.g. masturbatory madness) and current (e.g. DSM-5's Disruptive Mood Dysregulation Disorder – a formalised depressive disorder which is defined by irritability and temper outbursts while lacking any depressive symptom criteria). Again, despite BP-II's listing, there are many who doubt its existence, most commonly positioning it simply as a milder expression of a bipolar disorder spectrum or as a personality style marked by emotional dysregulation or normative mood swings (qua cyclothymia).

A key objective of this book is to argue directly and indirectly for its existence. Simply offering a 'believing is seeing' argument is scientifically unacceptable. Instead, any argument for its entity status requires BP II disorder to be defined by a number of clinical symptoms (both in relation to hypomanic and depressive states) that, as a set, are distinctive and not able to be positioned as simply reflecting a personality style. Failure to identify its status as a categorical mood disorder has contributed to its remaining under the radar. For example, in a recent paper (Parker *et al.*, 2017) we considered its coverage in a large set of evidence-based guidelines for managing bipolar disorders. Most made no reference to the condition. Of those making reference, few offered any specific recommendations for managing bipolar II, and most offered an 'extrapolation' management model (i.e. recommending the same medications as for those with a BP I condition). The structuring of those guidelines again provides evidence suggesting that there is limited recognition of the existence of BP II disorder and, secondly, if conceded, that the dominant model is a dimensional one.

Separate chapters in this book allow authors to debate its status either as a *dimensional* condition (reflecting a milder state lying on a spectrum that, at the more severe end, captures BP I disorder) or as a *categorical* condition separate from bipolar I disorder. Its 'existence' would be advanced if a substantive case can be made for its status as a categorical condition. Two chapters focus on offering arguments for each model. I favour a categorical binary model as detailed in Chapter 4, albeit recognizing the limitations to any simple binary model. For example, one wit stated that: '*There are two classes of people in the world: those who divide the people in the world into two classes and those who do not*'. Another wit (qua twit) observed '*There are only ten types of people in the world. Those who understand binary and those who don't*'.

There are major consequences to establishing whether BP II disorder differs dimensionally or categorically from BP I disorder. If the two conditions lie along a dimension, then it might be anticipated that the same management models would be relevant to each condition (i.e. the extrapolation model). If BP II disorder differs categorically, then it may respond quite differently to medications established as beneficial for those with a BP I disorder subject to the studies employing rigorous methodologies.

In relation to the last point, we have prepared a new chapter (Chapter 10) reviewing a number of major limitations to the design of studies evaluating the efficacy of treatments for the bipolar disorders, capturing key issues detailed in a recently published paper (Parker and Tavella, 2018), and limitations that are particularly salient in relation to BP II disorder. The short duration of many trials, the tendency to test mood stabilizers during acute episodes as against testing their efficacy as maintenance treatments, the many limitations to the measures most commonly applied and the frequency of their administration, all confound and limit our capacity to truly evaluate whether a treatment modifies both the highs and lows of a bipolar condition. Such limitations are particularly salient in evaluating interventions for BP II states when mood oscillations are more frequent in terms of episode frequency, duration and severity, and in assessing the comparative efficacy of differing management strategies.

There also remains a clear *need to improve detection and diagnosis*. BP II disorder seemingly attracts two positions – 'over-diagnosis' (often by expanding the spectrum or dimensional model into domains of personality and temperament) and 'under-diagnosis'. The latter concern is worthy of extension. As noted throughout the book, very high percentages of individuals with a BP II disorder never receive that diagnosis over their lifetime – and instead are most often diagnosed and managed as if they have a unipolar depressive disorder or given a personality disorder diagnosis (most commonly 'borderline'). For those who experience a distinct delay to obtaining a BP II diagnosis, the risks are of considerable 'collateral damage' from the condition (in terms of disruption to work and relationships in particular), of 'social suicide' (from engaging in activities that permanently damage the individual's reputation) and of actual suicide. Over the last decade I continue to be surprised by the high rates of colleagues who have failed to diagnose a seemingly characteristic BP II condition, either by neglecting to screen for the possibility during routine consultations or, sadly, when a patient seeks confirmation of such a diagnosis from a professional who does not accept or concede the existence of a BP II disorder.

I suspect that one of the principal explanations for 'failure to detect' is training – or, in this instance, the lack of it. Most psychiatrists train in facilities where they observe psychotic BP I states. Few mental health professionals over the age of forty have ever received a lecture on BP II disorder during their training course. Most professionals who have developed an interest in this diagnostic condition over the last few decades have generally 'learned on the job', observing a condition that varies in so many ways from BP I disorder. But perhaps the most common reason for failure to so diagnose is – as noted earlier – simply not asking screening questions for all patients who present for assistance with 'depression'. There is therefore a need for much greater professional and community awareness, and this has proceeded to a reasonable degree in Australia over the last decade following orthodox educational strategies and especially from prominent people in the community detailing features of their BP II condition in the media, a process encouraged by Stephen Fry's 2006 BBC series 'The Secret Life of the Manic-Depressive'. Such concerns argue for readily available assessment tools and that health professionals screen all patients presenting with signs and symptoms of 'depression' for the presence of a bipolar disorder.

Finally, there is the key issue of *management*. Evaluating management options is generally advanced by assessing 'the evidence'. In psychiatry, as in medicine, there is a generally accepted hierarchy or clinical evidence pyramid. Low-level 'evidence' is provided by ideas, opinions and case reports. At the next level lie case series, as well as both case

control and cohort studies. At the next level lie randomised controlled studies. At the highest level lie systematic reviews of the aggregated evidence and which are often supported by quantifying meta-analyses.

Low-level evidence is easy to criticize as, for example, it may simply reflect idiosyncratic opinion (and which may be erroneously persuasive simply if 'eminence-based'). But high-level evidence also has its limitations. Such evidence can be skewed by a number of factors. For example, medications (such as lithium) that have been prescribed for an extended period have a theoretical advantage over newer medications, when the latter may have been evaluated in few studies. Medications that have been evaluated in multiple studies are likely to be recommended above those that have been minimally evaluated. Efficacy studies tend to weigh evaluating benefit with less attention to 'costs' (i.e. side-effects). Findings from efficacy studies (most commonly generated from randomized controlled studies) may not cross-walk to real world clinical practice, most commonly reflecting the composition of those who take part in clinical trials. Trial participants tend to have milder disorders (with suicidal ideation being a representative exclusion criterion), may sometimes only enter the trial to obtain medication for free, are judged to have no history of drug or alcohol problems, no co-morbid symptom states or personality disorder, and are therefore quite pristine in comparison to those who attend clinical psychiatrists. Thus, randomized controlled trials and meta-analyses provide some evidence about the degree to which a medication works and may (subject to all potential side-effects being inquired about) provide important information about rates of risks and side-effects. But the actual 'effectiveness' of a medication in a clinical setting is generally not able to be assessed from such studies.

A common approach by clinicians is therefore to prescribe a medication to a set number of their own patients. If the medication is likely to be effective, the clinician may only require a dozen or so patients to obtain an effectiveness 'signal'. If a signal is not obtained until 20–50 patients have received the medication, then its real-world utility is likely to be low. A second common approach by clinicians is to ask a small set of 'experts' (i.e. clinician researchers who have prescribed the medication to a large number of patients) for their evaluation of the particular medication. Subject to such experts not having a conflict of interest, such information can be highly informative. Thus, rather than management guidelines being derived *only* from randomized controlled trials, there is an advantage to an iterative process whereby the trial efficacy data is melded with the opinions of unbiased experts. This approach is addressed in several individual chapters, including a new chapter addressing perinatal nuances in relation to the prescription of medication in pregnant or breastfeeding women with a bipolar II disorder.

In the absence of clear prescriptive evidence-based guidelines for the management of BP II the abhorred vacuum can best be filled by the views of practitioners who are clinically skilled and observant until the evidence base is more definitive. This book therefore offers an iterative process for the reader. Separate chapters overview and evaluate the efficacy data from clinical trials of differing medications, before offering a series of commentaries and where the commentators offer their clinically weighted observations. We encourage the reader to make their judgments on the basis of those two 'worlds' of evidence.

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Chapter 2

Bipolar Disorder in Historical Perspective

Edward Shorter

Bipolar disorder is, in a sense, as old as the hills. Yet its diagnosis as a distinct disorder is quite recent. Physicians have always recognized alternating states of melancholia and mania. It would be as idle to ask who was the first to describe this alternation as it would be to ask who first described mumps. Aretaeus of Cappadocia, around 150 years after the birth of Christ, wrote of the succession of the two illnesses. It is clear from the context (Jackson, 1986, pp. 39–41) that he was using the two terms to describe what we today would consider mania and melancholia. Yet Aretaeus did not consider the alternation of mania and melancholia to be a separate disease. Etienne Esquirol, director of the Charenton asylum outside of Paris and one of the founders of modern psychiatry, noted in 1819 (Esquirol, 1819, p. 169), 'sometimes melancholia passes into mania; indeed it is the ease with which this … transformation occurs that has led all the authors to confuse melancholia with mania'. There is no hint in Esquirol's writing that he considered the alternation of melancholia and mania to constitute a separate disorder.

For these remote centuries I use 'bipolar disorder' to mean the succession of melancholia and mania. A word of clarification: in the twentieth century, after the writing of Kleist and Leonhard, 'bipolar disorder' implies that there is a separate unipolar depressive disease. By contrast, the term 'manic-depression' suggests that there is only one depression, whether linked to mania or not. But the term 'manic-depressive insanity' itself did not surface until 1899. To describe mania, melancholia, and their alternation in previous centuries, I shall simply call it bipolar disorder and crave the reader's indulgence.

So the big question is not who first described bipolar disorder, but rather if it is one disease or two? The centuries of clinical experience that lie behind us constitute a mountain of evidence of some weight. And in this tremendous accumulation of practical learning, has bipolar disorder been considered one disease? Or two: the alternation of two separate diseases, mania and melancholia? A third possibility: is bipolar disorder an alternation of several different kinds of mood disorders that includes episodes of catatonia, melancholia, psychotic depression, mania, and hypomania, each an independent illness entity in its own right? Conrad Swartz has suggested that, in this kind of alternation, the term 'multipolar disorder' might be more appropriate than 'bipolar disorder' (Swartz, personal communication, 24 October 2006). When we find these syndromes occurring over the years in the same patient, is it one illness or several?

For psychiatrists of the past, it was quite common to see melancholia cede to mania. Vincenzo Chiarugi, a psychiatrist at the Bonifazio mental hospital in Florence, Italy, at the end of the eighteenth century, described a female patient, aged 35, who switched from deep melancholia to mania. Chiarugi thought this a case of 'true melancholy' and

by no means out of the ordinary. The clinicians of the day often used such terms as mania and melancholia in a sense quite different from ours, yet, on the basis of the case report (Chiarugi, 1794, pp. 95–6), Chiarugi was dealing with manic-depression.

In the world of patients as well, alternating mania and melancholia have been known since time out of mind. As Thomas Penrose, the curate of Newbury in Berkshire, England, penned (Penrose, 1775, p. 19) in the 1780s of a young woman disappointed in love:

> *Dim haggard looks, and clouded o'er with care,*
> *Point out to Pity's tears, the poor distracted fair.*
> *Dead to the world – her fondest wishes crossed*
> *She mourns herself thus early lost.*
> *Now, sadly gay, of sorrows past she sings,*
> *Now, pensive, ruminates unutterable things.*
> *She starts – she flies – who dares so rude*
> *On her sequester'd steps intrude?*

In the Voitsberg district of Austria early in the nineteenth century, such alternations of melancholia and mania were regarded by the valley dwellers as quite typical, and one of the features that distinguished them from the hill dwellers. Said a Dr. Irschitzky in 1838, 'We know from experience, that among the valley folk now and then melancholia occurs, mostly for religious reasons, and frequently acute insanity (mania). These mental illnesses follow in a quite natural manner from the constitution and the character of these people … whereby frequently mania serves as an interlude' (Irschitzky, 1838, p. 243).

These authors regarded mania and melancholia as two illnesses succeeding each other. Among the first observers to see this alternation of mania and melancholia as parts of the same disease was Spanish court physician Andrés Piquer Arrufat, who described in 1759 the mentally ill king Fernando VI has having 'el afecto mélancolico-maniaco', and penned a quite careful clinical description. Piquer regarded the illness as a unitary condition ('son una misma enfermedad') different from either melancholia or mania, in the broad sense in which those diagnoses were then understood (Piquer, 1759/1846, pp. 6, 27). Piquer's manuscript account was, however, not published until 1846, which makes his priority a bibliographic curiosity rather than a fundamental building stone in the history of psychiatric illness classification. Jésus Pérez and co-workers, who have studied the Piquer account carefully, point out that Piquer apparently launched the diagnosis in a 1764 textbook, yet without the careful characterization of it that we find in the memoir published in 1846 (Pérez et al., 2011, p. 72), nor do they mention the 1846 publication.

In 1818, German psychiatrist Johann Christian August Heinroth in Leipzig proposed four versions of 'mixed mood disorders' (gemischte Gemüthsstörungen), in each of which some kind of insanity alternated with melancholia. One form, for example, Heinroth described as the alternation of 'madness' (Wahnsinn) and melancholia. Calling the disorder 'quiet madness (ecstasis melancholica)', Heinroth said that in the illness, madness 'loses its monstrousness', and melancholia loses its 'lifelessness, and the whole illness proceeds in alternating exaltation and depression'. Heinroth also threw in a dollop of German romanticism, and had the patient spending the melancholic phase 'dragging about the fields and woods or isolated mountain tops giving full expression to his still sobs and sighs, or weaving in quiet contemplation wreaths of white flowers …' (Heinroth, 1818, pp. 355–6).

By the 1840s such accounts were numerous. In 1844, Carl Friedrich Flemming, director of the Sachsenberg mental hospital in Germany, described '*Dysthymia mutabilis*', the kind of mood disorder that arises when *Dysthymia atra* (black depression) and *Dysthymia candida* (low-level mania) alternate. 'Between both of them (atra and candida) there is a not infrequent connection, *Dysthymia mutabilis*, which sometimes shows the character of one, sometimes the character of the other'. Flemming saw other kinds of depression too, such as *melancholia attonita*, or stuporous melancholia (Flemming, 1844, pp. 114, 129).

Flemming's proposed coinage, appearing in a then obscure German language journal, was soon forgotten in an era when Paris was the centre of the enlightened world. And it was in Paris that bipolar disorder as a separate entity was famously announced a few years later. In 1850 Jean-Pierre Falret, a staff psychiatrist of the Salpêtrière Hospice in Paris gave a lecture to the Psychiatric Society in which he briefly mentioned 'circular insanity' (*la folie circulaire*), thus giving the alternation of mania and melancholia a separate name. He incorporated the idea into the clinical lectures he offered at the hospital in the early 1850s and published those lectures in 1854. Whatever Falret might have said in the early lectures, by the 1854 book, the alternation of mania and melancholia in *la folie circulaire* had become a disease of its own, not just the succession of two separate illnesses. Falret: '[La folie circulaire] is generally neither mania nor melancholia as such, with their customary characteristics; it is, in some manner, the core of these two kinds of mental disease without their depth [*sans leur relief*]' (Falret, 1854a, pp. 249–50). He went on to explain how bipolar mania and melancholia differed from the regular versions. There was in 1854 a vigorous exchange between Jules Baillarger, who claimed to have described the same disease under another label (*la folie à double forme*), claiming priority, and Falret, who insisted on his own priority of *la folie circulaire* (Baillarger, 1854a, 1854b; Falret, 1854b).

In 1864, Falret attempted to strangle the entire debate by insisting that neither mania nor melancholia existed as separate diseases and the only natural entity was *la folie circulaire*, in which these phases alternated, sometimes at prolonged intervals (Falret, 1864). The issue of which of these squabbling clinicians has priority is secondary. But it would be fair to say that in Paris in the early 1850s bipolar disorder was born for an international audience, yet without the careful apparatus of psychopathology and nosology that came later.

The baton now passed to the Germans, and for the next hundred years the principal contributions to bipolar disorder would be made by German professors. In 1878 Ludwig Kirn, a psychiatry resident who had trained at the Illenau asylum, published a postdoctoral thesis on 'the periodic psychoses' in which he gave a detailed psychopathological account of bipolar disorder, something the French clinicians had omitted in favour of grand generalizations (Kirn, 1878). German nationalists, with their dislike of the French, considered this the first description of the disorder *tout court*, but it in fact was not (Kirchhoff, 1924, p. 167).

In these years many German psychiatrists such as Wilhelm Griesinger and Heinrich Neumann described bipolar disorder in one form or another. For most, the usual course was switching from melancholia into mania, and then into terminal dementia, more or less as Falret had first described. But in 1882, Karl Kahlbaum, one of the great names in the history of German psychiatry – because of his insistence on using the 'clinical method' to study psychopathology – proposed the term 'cyclothymia' for recoverable alternations of melancholia and mania. Yet these cases did not tip into dementia (as in Heinrich Neumann's 'typical insanity'). Instead, the patients got better.

Another such cyclical episode might then occur, and so forth. Also, the 'mania' that Kahlbaum described was not a full-blast onslaught affecting all mental functions but a kind of exaggerated elation without psychosis (Kahlbaum, 1882). It corresponded roughly to what Berlin psychiatrist Emanuel Ernst Mendel had a year previously called 'hypomania' (Mendel, 1881), and is – in essence – the ancestor of 'bipolar II disorder'.

Then came the great earthquake in German nosology: Emil Kraepelin and his historic classification of psychiatric illnesses, the basic outlines of which have endured more or less intact until the present. The classification, based on course and outcome, became the first real conceptualization of manic-depressive illness, a disease having an undulating course rather than an irreversible downhill slide as in chronic psychosis (which Kraepelin called '*dementia praecox*'). Building on the work of Kahlbaum in 1863 – who was the first psychiatrist to have classified mental illnesses on the basis of clinical course (Kahlbaum, 1863) – Kraepelin spelled out the importance of illness course in detail for mania and melancholia. Thomas Ban once observed, 'Many people described what was to become manic-depressive illness but it was Emil Kraepelin who conceptualised it as a class of illness because of his adoption of temporality as an organizing principle of psychiatric nosology' (Ban, personal communication, 9 November 2006).

In 1899, in the sixth edition of his textbook, Kraepelin lumped together all depression (except that beginning in middle age) and all mania under the category manic-depression (Kraepelin, 1899). For him, it was the sole mood disorder. There was no 'unipolar' depression. Kraepelin thought it a matter of indifference whether the illnesses recurred periodically, or whether mania and melancholia were linked together or not. Thus, with Kraepelin's work what we most emphatically call 'bipolar disorder' ceased to be a separate disease. The concept of alternating mania and melancholia as a disease of its own became lost from sight because Kraepelin considered *all* mood disorders to be part of 'manic-depressive insanity' (*das manisch-depressive Irresein*). Although we commonly say that bipolar disorder is the successor of Kraepelin's manic-depressive insanity, this is erroneous: Kraepelin incorporated all cases of depression and mania, alternating or not, into manic-depression. By contrast, our use of the term 'bipolar disorder' implies that there is a separate class of unipolar depression.

Two further comments about Kraepelin's manic-depressive illness should be made. Firstly, in later editions, he popularized Wilhelm Weygandt's concept of the existence of 'mixed psychoses'; that is, manic and depressive symptoms appearing simultaneously. Weygandt had ventured the notion in a post-doctoral thesis, which was not an automatic guarantee of international acceptance (Weygandt, 1899, 1904).

Secondly, Kraepelin doubted that Kahlbaum's cyclothymia represented a separate illness but was rather just a form of manic-depressive insanity in which there might be long lucid intervals between episodes. Today's *Diagnostic and Statistical Manual* (DSM-5) positions cyclothymic disorder as separate from the main bipolar disorders (I and II) because the hypomania and depression of cyclothymia both fall below the threshold of a full episode of mania or of major depression (American Psychiatric Association, 2013).

The main problem with Kraepelin's manic-depressive illness was not its nosological adequacy – there is really no reason why the concept would not serve us quite well today – but its prognostic desperateness: Kraepelin had a dim view of the prognosis of most illnesses. He believed that dementia praecox went relentlessly downhill, but that lifetime prospects for 'MDI' were those of unceasing recidivism. Oswald Bumke, soon to succeed Kraepelin as Professor of Psychiatry in Munich, wrote in 1908, 'Many physicians

today view the chances of recovery of a patient who once falls ill with mania or melancholia as far too unfavourably – because a relapse is possible but certainly not necessary' (Bumke, 1908, p. 39). Of treatment in those days there was, with the exception of opium for melancholia, very little talk.

The next development was elaborating the 'two depressions', the depression of unipolar disorder and the depression of bipolar disorder. Kraepelin taught in Heidelberg and Munich. But the charge back towards bipolar disorder as a disease of its own, *à la Française*, began in a different academic fortress entirely: Karl Kleist's university clinic in Frankfurt. Kleist was not an adept of Kraepelin and his circle identified with the intensely biological approach to psychiatry of Carl Wernicke. It was actually Wernicke (1900) who adumbrated in part three of his textbook, published in 1900, the first of these new bipolar entities: hyperkinetic and akinetic motility psychosis.

For Wernicke, bipolarity was not a major issue. But for Kleist it was. Kleist's ambition was to continue the series of independent disease entities between manic-depressive illness and dementia praecox, which were the two great diseases that Kraepelin had established. Between these bookends, Kleist (1911) started to insert a number of diagnoses, some unipolar and some bipolar. It is therefore Kleist who restored bipolar thinking to psychiatry in 1911, without challenging the existence of Kraepelin's manic-depressive illness (which was, of course, not a bipolar illness because Kraepelin did not conceptualize a separate unipolar depression).

In the following years Kleist identified several other cyclical psychoses, including 'confusional psychoses' that alternate between 'agitated confusion' and 'stupor' (Kleist, 1926, 1928). The point was, for Kleist and other investigators in these years, to open up space in between Kraepelin's two great diseases, which were manic-depression and dementia praecox, to find room in the middle for diagnoses with prognoses that were perhaps more benign than Kraepelin's terrible dementia praecox. Yet, against the great Kraepelinian 'two-disease' tide, Kleist's ideas made little headway at this point.

Kleist had two very productive students, Edda Neele and Karl Leonhard, who after the Second World War carried forward Kleist's teachings about bipolarity. In a 1948 textbook, Leonhard said, 'Manic-depressive or circular insanity demonstrates two poles, which are characterized through the manic phase or mania and the depressive phase or melancholia'. Leonhard used the term 'bipolarity' (*Bipolarität*) (Leonhard, 1948, p. 88). Then in a 1949 study of all 'cyclical psychoses' admitted to the Frankfurt university clinic between 1938 and 1942, Neele (1949, p. 6) reinforced the terms 'unipolar disorder' and 'bipolar disorder' (*einpolige und zweipolige Erkrankungen*). Kleist must have used these previously in a teaching setting but Neele's post-doctoral thesis (*Habilitation*) is their first major public airing.

Throughout the 1940s and 1950s Leonhard burrowed away at the periodic and the cyclical psychoses – at Frankfurt until 1955, then at Erfurt and Berlin – trying to insert them in the larger scheme of psychiatric illness. In 1957, Leonhard's magisterial study – *The Classification of the Endogenous Psychoses* – appeared and definitively separated what we call bipolar affective disorder from 'pure depression'. This separation of depressive illness by polarity remains in force in most circles today. 'Undoubtedly there is a manic-depressive illness', wrote Leonhard (1957, pp. 4–5) 'having in its very nature the tendency to mania and melancholia alike. But next to this there are also periodically appearing euphoric and depressive states that show no disposition at all to change to the opposite form. Thus, there exists this basic and very important distinction between bipolar and