JANUSZ RYBAKOWSKI

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THE AMAZING DRUG IN PSYCHIATRY

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Lithium – The Amazing Drug in Psychiatry
Janusz Rybakowski

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CHAPTER 1

Kraepelin's classification of mental disorders and the author's case

There is no doubt that in mania patients' improvement has closely paralleled treatment and that this criterion has been fulfilled in the chronic and subacute cases just as closely as in the cases of more recent onset. (...) The effect on patients with pure psychotic excitement – that is, true manic attacks – is so specific that it inevitably leads to speculation as to the possible etiological significance of a deficiency in the body of lithium ions in the genesis of this disorder.

John F. Cade. "Lithium salts in the treatment of psychotic excitement". Medical Journal of Australia, 1949.

The above statements come from an article written by an Australian psychiatrist, John Cade, concerning the administration of lithium carbonate to 10 manic patients, which was published 70 years ago[67]. It is believed that this publication marks the date of introduction of lithium as a therapeutic agent into modern psychiatry. It can also be considered as the beginning of modern psychopharmacology, because it was three years ahead of the work of French psychiatrists announcing the introduction of the first neuroleptic (antipsychotic) drug – chlorpromazine, in patients with schizophrenia[87]. Whereas in the second half of the 50s, a work was published by Swiss psychiatrist Roland Kuhn which can be considered an introduction of tricyclic antidepressants into psychiatric treatment[219].

Over time, both antipsychotics and antidepressants have seen the introduction of a new generation of these agents. With regard to the former, these are atypical antipsychotic drugs introduced into medical treatment in the 1990s. The second generation of antidepressants could be considered the introduction of selective serotonin reuptake inhibitors (SSRI), which are currently the most commonly used antidepressants. The demonstration of the prophylactic effect of lithium in affective disorders in the first half of the 1960s triggered the introduction of

the first generation of mood-stabilizing drugs, for which lithium was the prototype. The second generation of mood-stabilizing drugs was introduced into psychiatric treatment more than 20 years later.

Cade's paper features two distinctive elements. In the first of them, the author confirms the therapeutic effect of lithium in manic patients. In patients with chronic manic symptoms, spontaneous remission of symptoms can sometimes be suspected due to the periodic character of the disease (manic-depressive disorder). On the other hand, in patients in the state of acute mania, the improvement, sometimes spectacular, should undoubtedly be attributed to the effects of lithium. Two years later, the anti-manic effect of lithium in over 30 patients was described by other Australian researchers[275]. Whereas five years later, Danish psychiatrist Mogens Schou, who is the protagonist of one of the subsequent chapters of this book, confirmed the anti-manic effects of lithium in more than 30 patients, assessing the drug's efficacy using placebo[393].

In the second part of the cited text, Cade considers whether, due to such a specific therapeutic effect of lithium, its deficiency in the body is significant in the pathogenesis of the manic state. This is a speculation on the biological significance of lithium in humans as a so-called trace element. Subsequent studies on endogenous concentration of lithium in the body have shown that it is very low and amounts to several micromoles per litre[229]. Whereas the therapeutic concentration of lithium, obtained by administering lithium preparations, is about 200 times higher. Therefore, it can be assumed that the endogenous concentration of lithium is not significant for treatment with lithium salt preparations. Cade's speculation on the pathogenic significance of lithium deficiency in the body was, however, validated to a certain extent in the 21st century, when it became apparent that trace concentrations of lithium may be significant for some aspects of mental health. This is discussed in Chapters 16 and 20.

The effect of lithium salts on mental functions was first observed in the second half of the 19th century, when Danish doctor and scientist Carl Lange proposed the use of lithium carbonate in the treatment of periodic depression[223], while American doctor William Hammond attempted to administer lithium bromide to manic patients[150]. But we could even go back to ancient times in this respect and talk about the recommendations of a famous Roman physician, Soranus of Ephesus, who lived in the 2nd century. He recommended a method of treatment of nervous disorders consisting in drinking alkaline water. As it later turned out, such water contains a significant amount of lithium ions[129].

Following Cade's publication, the use of lithium salts in affective disorders, characterised by periodic mood and activity disorders, for 70 years has been the subject of intensive experimental and clinical research. A significant event connected to the therapeutic effects of lithium administration was the demonstration of the very beneficial effect of this ion on the long-term course of affective disorders, i.e. prevention of recurrence of both mania and depression. The first article, which indicated the prophylactic efficacy of lithium in these

disorders, was published in 1963 and was written by British psychiatrist Geoffrey Hartigan[153].

Lithium is one of the first three elements that emerged in the creation of the universe, with atomic number 3 in Mendeleev's Periodic Table. The fact that such a simple cation can have such a powerful effect on the human mind, especially in a therapeutic context in psychiatry, remains a great mystery to modern science. Most psychiatrists agree that 70 years after Cade's publication, lithium remains one of the most important drugs in psychiatry. Many of them also believe that its use in patients with affective disorders is insufficient and, if lithium was used appropriately, a much larger number of such patients could get the best help. This book attempts to describe the phenomenon of lithium in psychiatry in both theoretical and practical aspects. This chapter discusses the therapeutic effects of lithium in the context of the so-called Kraepelin's classification of mental disorders, which preceded Cade's famous article by 50 years.

As mentioned above, half a century before Cade's publication, that is exactly 120 years ago, the sixth edition of the psychiatry handbook written by the great German psychiatrist Emil Kraepelin was published. At that time, Kraepelin was a psychiatry professor and the head of the psychiatric clinic at the University of Heidelberg. Kraepelin created a fundamental dichotomous classification of major mental disorders, which shaped psychiatric diagnostics for the whole of the 20th century, and some of its elements are still valid today[212]. He distinguished two groups of mental disorders on the basis of chronic or periodic course of the disease and presence of impaired cognitive processes. The first of them, in which he included patients with a chronic course of the disease and systematic cognitive deterioration, he called *dementia praecox*. 12 years later, Swiss psychiatrist Eugen Bleuler proposed the term "schizophrenia" to describe this group, which is still used today[51]. The second group of mental disorders, characterised by a periodical course of the disease and relative stability of cognitive processes, was called by Kraepelin *manisch-depressives Irresein*, which can be translated as manic-depressive disorder. This group was characterised by periodic occurrence

Figure 1. Emil Kraepelin (1856-1926), great German psychiatrist, creator of a fundamental classification of mental disorders into *dementia praecox* and *manisch-depressives Irresein*

of polar opposite disorders, namely mania and depression. Such psychopathological syndromes correspond, according to the current terminology, to "affective disorders", also referred to as *mood disorders*. Kraepelin's *manisch-depressives Irresein* included both periodic depressions and disorders with periodically occurring manic and depressive states. With regard to the latter, the name "manic-depressive psychosis" was introduced.

Later in life, Kraepelin himself admitted that there was a group of patients that could not be clearly assigned into one of the abovementioned groups[213]. And just a few years later (1933), the concept of "schizoaffective psychosis" was proposed by Jacob Kasanin (1897-1946), an American psychiatrist of Russian origin. According to Kasanin, schizoaffective psychosis is periodic in nature and shows symptoms of both schizophrenia and affective disorders[189].

A significant event in the history of psychiatric classifications of the 20th century was separation of unipolar and bipolar affective disorders. The precursor of the approach taking into account the phenomenological polarity of affective disorders was German psychiatrist Karl Kleist (1879-1960), who differentiated between unipolar affective disorders (German: *einpolig*) and bipolar disorders (*zweipolig*). Whereas another German psychiatrist Karl Leonhard (1904-1988) created an extremely precise description of various forms of periodic affective disorders, which he called "phasic psychoses" and "cycloid psychoses". He distinguished bipolar psychoses: manic-depressive and cycloid, and monopolar psychoses: melancholy, depression, euphoria and mania[230].

Observations and studies on the personality traits of patients with these diseases also became grounds for distinguishing between bipolar and monopolar affective disorder. Back in the 1920s, German psychiatrist Ernst Kretschmer (1988-1964) used the term "cyclothymia" to describe the physical and personal characteristics of patients with bipolar manic and depressive states. It was supposed to indicate a specific personality profile predisposing patients to the development of manic-depressive psychosis[217]. More than 40 years later another German psychiatrist, Hubertus Tellenbach (1914-1994), presented a per-

Figure 2. Jacob Kasanin (1897-1946), American psychiatrist of Russian origin, creator of the concept of schizoaffective psychosis

sonality concept with a dominant depressive component, which he called *typus melancholicus*. People with such personality were supposed to be more susceptible to "unipolar" depressive states[440].

In 1966, the results of studies by two psychiatrists were published: Jules Angst from Switzerland and Carl Perris, a psychiatrist of Italian origin working in Sweden. Both of them, independently of each other, showed a different character of the occurrence of mental disorders in families of patients with uni- and bipolar affective disorder[11,298]. They found that in families of patients with unipolar disorder there were almost exclusively cases of unipolar disorder, while in families of patients with bipolar disorder – mainly bipolar cases. Moreover, the incidence of mental disorders in families of patients with bipolar affective disorder was much higher than in families of patients with unipolar disorder. According to these authors' concepts, bipolar affective disorder corresponded to the previous concept of manic-depressive psychosis, whereas unipolar affective disorder was understood by both authors as recurrent depressive episodes, without the occurrence of manic episodes. Thus, the criterion for diagnosing bipolar affective disorder became occurrence of manic episodes in both patients and their families.

With regard to the last two researchers, it should be noted that Carlo Perris (1928-2000) also dealt with the issue of cycloid psychoses[299], previously mentioned in the context of Karl Leonhard's research, i.e. bipolar psychoses, often with symptomatology similar to schizophrenia, which may fall in the middle between schizophrenia and affective disorders. He even proposed diagnostic criteria including a brief acute psychotic episode with accompanying bipolar symptoms of mood disorders, sometimes also with disorders of consciousness[300]. He hoped that in the emerging international classification of diseases, ICD-10, cycloid psychosis would be featured as a separate diagnostic entity, but his expectations were not realised.

Jules Angst is one of the most prominent researchers studying affective disorders. In addition to previously mentioned genetic studies, which provided the basis for the differentiation between unipolar and bipolar affective disorder, Angst developed a diagnostic concept for brief recurrent depression[12], brief hypomania[13], and supported the classification of unipolar mania as a separate diagnostic entity[17]. In 2016, his 90th birthday was greatly celebrated in Zurich. Five years ago Jules Angst was the main lecturer at the "Neuropsychiatry and Neuropsychology. 2014 Update" conference, held in Poznań on 27-28 November 2014, which was co-organised by Termedia, the publisher of this book. At the conference he delivered a lecture on the epidemiology and classification of affective disorders.

Research on schizoaffective disorder carried out at the beginning of the 21st century, i.e. more than 80 years after the introduction of this term by Jacob Kasanin, did not bring any definite conclusions as to the diagnostic position of this disorder. Brazilian researchers conducted a systematic review of 49 papers comparing schizoaffective disorders with schizophrenia and affective disorders. On the basis of the analysis of demographic, clinical, biochemical, genetic, neu-

roimaging and pharmacological factors, they concluded that schizoaffective disorder falls between schizophrenia and affective disorders. However, it cannot be interpreted as an atypical form of schizophrenia or affective disorder, as a comorbidity or a separate mental disorder, but rather as a heterogeneous group composed of patients with both schizophrenia and affective disorders, falling somewhere between these diseases[73]. A tool was also developed – *Schizo-Bipolar Scale* – measuring the type and proportion of psychotic and affective symptoms, used on 762 patients with psychotic disorders such as schizophrenia, schizoaffective disorder and bipolar affective disorder with psychotic symptoms. It turned out that in 45% of the patients the results were on the continuum between schizophrenia and bipolar disorder[194].

American authors have assessed, in several hundred patients, the correlation between the symptoms and the long-term course of the disease, constituting one of Kraepelin's classification criteria, as stated above. They found that the symptoms of psychosis without affective disorders were connected to much greater deterioration of general functioning, periodic mania symptoms indicated a better prognosis as compared to chronic mania or no mania symptoms, while both the duration of depression and psychosis symptoms correlated with a worse prognosis. The authors believe that the results may confirm Kraepelin's dichotomous concept[211].

Modern diagnosis of affective disorders is based on diagnostic criteria developed as part of the International Classification of Diseases, currently edition 10 (ICD-10)[163], and on the criteria set out by the American Diagnostic and Statistical

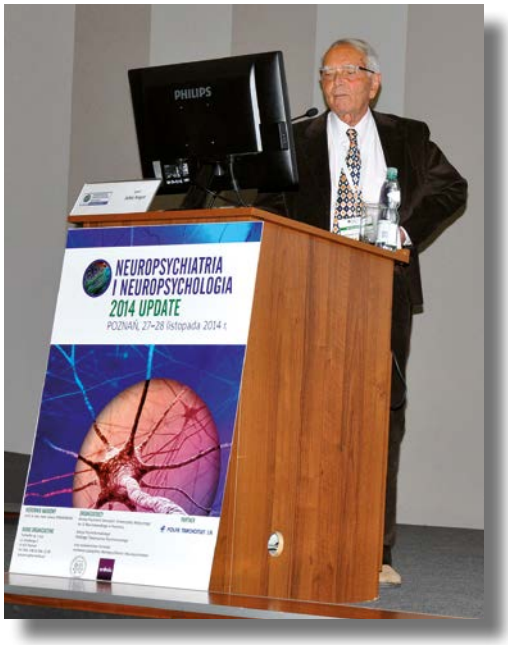


Figure 3. Professor Jules Angst at the "Neuropsychiatry and Neuropsychology" conference in Poznań, 2014

Manual, version five (DSM-5)[92]. The ICD-10 version was published in 1992 and has been applied in Poland since 1997. In the chapter dedicated to affective disorders (mood disorders), manic-depressive disorder is listed as a bipolar affective disorder, code F31. Periodic recurrent depression (unipolar affective disorder) is defined as a recurrent depressive disorder, code F33. Whereas code F32 stands for the first depressive episode, when it is not yet known whether bipolar or unipolar affective disorder will develop further in the course of the disease. Schizoaffective disorder coded as F25 was included in the chapter on schizophrenia, schizotypal and delusional disorders. In contrast, cycloid psychoses were included under code F23 as acute and transient psychotic disorders in subsection "acute polymorphic psychotic disorders without symptoms of schizophrenia".

Fourth edition of the American mental disorder diagnostic system (DSM-IV)[91] was published in 1994 during the convention of the American Psychiatric Association in Philadelphia. It took place on the 150th anniversary of the founding of the pioneering organisation of this association, known as the Association of Medical Superintendents of American Institutions for the Insane, which later changed its name to the American Psychiatric Association. In DSM-IV, in the chapter dedicated to mood disorders the term "major depressive disorder" is used. It can be interpreted as an episode of depression in the course of unipolar or bipolar affective disorder. Manic-depressive disorder is defined as a bipolar disorder, and the first episode of depression or recurring depression is referred to as "major depressive disorder". In DSM-5, bipolar affective disorders (manic-depressive) and depressive disorders, grouped together in DSM-IV under mood disorders, were classed as separate diagnostic categories[243]. In DSM-IV, schizoaffective disorder was placed in the group of schizophrenia and other psychotic disorders, and similarly in DSM-5 – in the spectrum of schizophrenia and other psychotic disorders. In terms of cycloid psychoses, in both diagnostic system versions the closest thing is brief psychotic disorder.

Since in his fundamental work Cade demonstrated the therapeutic effect of lithium in mania, it seemed that the main indication for lithium treatment would be manic episodes occurring in the course of manic-depressive psychosis. However, ground-breaking publications by Hartigan and his successors in the 1960s meant that in addition to treatment of acute mania, long-term administration of lithium began to be seen as an even more important indication for its therapeutic use, as it prevented the recurrence of affective disorders. Recurrence prevention was to concern both mania and depression. As already mentioned, in the second half of the 19th century Danish doctor Carl Lange used lithium salts to treat and prevent periodic depression. The antidepressant effects of lithium were also observed in clinical studies carried out in 1960-1980. One of such studies was conducted at that time at the Psychiatric Clinic at the Medical Academy in Poznań[335].

The confirmation of the effects of lithium, both therapeutic and prophylactic, on both psychopathological extremes, i.e. mania and depression, meant that the drug became a prototype of a new category of psychotropic drugs, whose effects

could be described as mood-stabilizing. In Polish, the term "normothymic drugs" is used. This term concerns therapeutic and/or prophylactic effects in the state of mania and depression, not causing deterioration in either of these states. In the 60s and 70s, alongside lithium, normothymic properties of anti-epileptic drugs were demonstrated, such as valproate and carbamazepine. These agents, together with lithium, can be described as 1st generation mood-stabilizing drugs. Whereas since the mid-1990s the mood-stabilizing properties of atypical antipsychotics, initially introduced to treat schizophrenia, have been documented. As a quarter of a century passed since the introduction of the first group of such agents, the latter can be classed as 2nd generation mood-stabilizing drugs. At that time, the mood-stabilizing properties of lamotrigine, a new anti-epileptic drug, were also confirmed[353].

100 years after Kraepelin presented a proposal for a dichotomous classification of the main mental disorders, i.e. in the 1990s, the concept began to be seriously questioned. One of the key pieces of evidence against it was the fact described above, namely that atypical antipsychotics with mood-stabilizing properties proved to be therapeutically effective in both schizophrenia and bipolar affective disorder. On the other hand, however, we have lithium, as a very specific medicine for affective disorders, whose antipsychotic effect or therapeutic efficacy in schizophrenia have never been demonstrated. It turns out that anti-epileptic drugs from 1st (valproate and carbamazepine) and 2nd generation (lamotrigine) of mood stabilizers do not have this effect either. Thus, both the psychotropic effects of lithium and of anti-epileptic drugs with mood-stabilizing properties may provide an argument in favour of Kraepelin's concept[382].

The second area that undermined the concept of Kraepelin's dichotomous classification of the main mental disorders was the results of genetic research. In terms of population genetics, probably the most important work was published by Swedish researchers, who studied 2 million families in Sweden and showed that patients with schizophrenia had an increased risk of also developing bipolar affective disorder, while patients with bipolar affective disorder had an increased risk of also developing schizophrenia[236]. In recent years, molecular genetics has gained a powerful tool, i.e. genome-wide association study (GWAS), which facilitates evaluation of one million and more polymorphisms of all 30,000 human genes. GWAS studies have shown a significant overlap of numerous genes predisposing the individual to develop both schizophrenia and bipolar affective disorder. At the same time, the existence of a somewhat distinct profile of genes predisposing people to the development of schizophrenia and bipolar affective disorder was also found[329]. Whereas in 2016 the results of the first GWAS study of genes related to the prophylactic efficacy of lithium were published[161].

The author of this book began his adventure with lithium almost half a century ago, in 1970, in the early days of his work at the Psychiatric Clinic of the Medical Academy in Poznań. That was the year when it became possible at the laboratory at the Poznań clinic to determine the concentration of lithium in bodily fluids (blood and urine), as well as in red blood cells. In the same year lithium carbonate

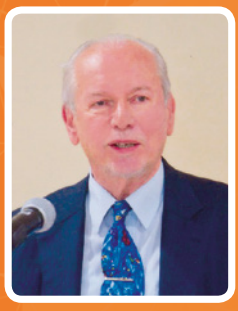
was started to be administered to patients with affective disorders for both therapeutic and preventive purposes. One of the patients, who was first given lithium in 1970, still continues this therapy today.

Already in 1972 the first publications on lithium therapy by the Poznań research centre came out. These concerned, among others, lithium poisoning[332], a case of diabetes insipidus, which occurred in the course of administration of lithium[333] and administration of lithium carbonate for therapeutic purposes in patients with so-called endogenous depression[334]. At that time, the author's doctoral dissertation entitled "A study of some aspects of water and electrolyte metabolism in patients with affective disorders treated with lithium carbonate" was also being prepared, which was defended in 1973.

Looking back almost half a century later on the author's road through psychiatry, the "lithium path" was usually one of the most important clinical and research threads. It resulted in the publication of 150 works oscillating around the subject of lithium. On the subsequent pages of the book, while discussing many lithium-related issues, extensive supplements to the text are presented, referring to the author's own works.

The recent monography of Professor Janusz Rybakowski titled "Lithium – the amazing drug in psychiatry" presents various faces of this element possessing astounding psychotropic properties. The author gives an account of the knowledge on mood disorders, and their treatment in the context of history and contemporary times of using lithium in these illnesses. He discusses the efficacy of lithium in the treatment and prevention of recurrences of mood disorders, the adverse effects and their management, pharmacokinetic and pharmacodynamic interactions as well as the biochemical mechanism of lithium action. In subsequent chapters, he depicts the issues of lithium administration during pregnancy and the postpartum period, lithium's anti-suicidal properties as well as antiviral, immunomodulatory, neuroprotective and "antidementia" activities. The book has been developed from a perspective of nearly half-century experience of the author with lithium.

Janusz Rybakowski



Born in Krotoszyn, in Wielkopolska (1946). A graduate of medical studies at the Poznań Medical Academy. A scholarship holder of the Fogarty Foundation in the Department of Psychiatry at the University of Pennsylvania in Philadelphia (1976-1977). Chairman of the Department of Psychiatry at Bydgoszcz Medical Academy (1985-1995). Head of the Department of Adult Psychiatry, Poznań University of Medical Sciences (1995-2016). President of the Polish Psychiatric Association (1998-2001). A member of numerous international scientific societies and editorial boards of Polish and foreign journals. Chairman of the Advisory Board of Psychiatria Polska. Editor-in-Chief of the journals "Pharmacotherapy in Psychiatry and Neurology" and "Neuropsychiatry and Neuropsychology".

The author and co-author over 700 scientific articles, most of them published in reputable scientific journals, and his Hirsch index is 53. A particular subject of his interest in medical practice and research is bipolar affective illness (manic-depressive), its pathogenesis and treatment, especially in the context of using lithium. He is a member of the editorial board of most important journals dedicated to bipolar illness such as "Bipolar Disorders" and the "International Journal of Bipolar Disorders". Recipient of prestigious scientific awards: in 2012, the Lifetime Achievement Award of the European Bipolar Forum, in 2015, the Lifetime Achievement Award in Biological Psychiatry of the World Federation of the Societies of Biological Psychiatry, and 2018, the Mogens Schou Research Award from the International Society of Bipolar Disorders.

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