

A half-century of participant observation in psychiatry. Part I: schizophrenia

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Summary

In three articles, I discuss the 50 years of my work in psychiatry, in the formula of so-called participant observation. The first one is about schizophrenia. I present important events of the pathogenesis and diagnostics in a recent half-century and my attempts to contribute to the research. Significant for clinical description was distinguishing the positive and negative symptoms of schizophrenia. The evidence for subcortical dopaminergic hyperactivity associated with positive (psychotic) symptoms, and prefrontal dopaminergic hypoactivity, responsible for mental deficits and cognitive impairment, has been obtained. Inhibition of the dopaminergic system (blocking of dopaminergic receptors D2) is the main therapeutic mechanism of antipsychotic drugs. Neurobiological and genetic data also pointed to the role of the glutamatergic system in schizophrenia, which prompted trials of pharmacotherapy. For more than 30 years, the neurodevelopmental hypothesis of schizophrenia, assuming the interaction of genetic and environmental factors, leading to the first psychotic episode, has been the most important pathogenetic concept. In the 1990s, under my direction, neurobiological studies on schizophrenia were performed in the context of positive and negative symptoms and differences vs. mood disorders. Verification of the niacin test, a possible diagnostic aid in schizophrenia, was also made. In the recent two decades, molecular-genetic studies in schizophrenia, also using cognitive endophenotypes and eye movements, have been performed. The association of the polymorphism of various genes with schizophrenia or its endophenotype has been demonstrated, frequently, the first time in the world. In recent years, I directed a team implementing the Polish versions of new scales for the assessment of negative symptoms of schizophrenia.

Key words: psychiatry, schizophrenia

Introduction

Fifty years ago, in 1970, I began to work at the Department of Psychiatry, Medical Academy in Poznan. During the next half-century, I have witnessed an evolution of contemporary psychiatry. I have been especially interested in pathogenetic concepts

of psychiatric disturbances as well as the possibilities of their treatment, mainly pharmacological ones. After some time of observation of what has been going on in current psychiatry, I attempted to make a more or less successful contribution to it. From such perspective, I would like to present three issues I have been mostly involved in, namely schizophrenia, affective disorders and psychopharmacology.

Studies on the pathogenesis of schizophrenia in the last half-century

To begin this triptych with schizophrenia seems justified as fifty years ago many psychiatrists considered schizophrenia as a 'queen' of psychiatry. Undoubtedly, patients with this diagnosis reigned on psychiatric wards, constituting a majority of inmates in these settings. Psychotic symptoms of schizophrenia were effectively treated with neuroleptic drugs, but frequently at the expense of disturbing extrapyramidal symptoms resulting in easy recognizability or, in contemporary understanding, 'stigmatization' of such patients.

Besides therapeutic possibilities associated with neuroleptic drugs, schizophrenia was still perceived as a 'functional' psychosis without the distinct organic brain substrate. However, due to the new methods of brain neuroimaging, its elements have been slowly identified. The paper of the British authors from the Northwick Park hospital in London should be recognized as groundbreaking in this respect (Eve Johnstone et al.) [1]. Using a newly introduced method of computer tomography, for which their compatriot, Godfrey Hounsfield, together with an American, Allan Cormack, received the Nobel Prize in 1979, they showed that patients with schizophrenia had an increased volume of cerebral ventricles, which correlated with the severity of cognitive impairment. This started a process of identification of brain changes in patients with schizophrenia, which have been confirmed in subsequent neuroimaging studies, both structural and functional.

In the 1980s, the clinical and pathogenetic concepts of schizophrenia appeared, which, practically, have been functioning until now. Each of them had a British originator and its counterpart on the other side of the Atlantic. The clinical concept was distinguishing the so-called positive (psychotic) and negative (deficit) symptoms among schizophrenic symptoms occurring in the same patient. It constituted some reconciliation of the views of Emil Kraepelin and Eugen Bleuler, favoring the symptoms of mental deficits (negative), and those of Kurt Schneider, who recognized psychotic (positive) symptoms as the first rank symptoms of schizophrenia.

On the European side, the proponent of the concept of positive and negative symptoms was Timothy Crow, from the already mentioned Northwick Park hospital. Crow thought that only positive symptoms respond to neuroleptic treatment while such a therapeutic reaction of negative symptoms is not present. Depending on the dominance of the positive or negative symptoms, he distinguished two types of schizophrenia [2]. Crow also suggested many pathogenetic theories for schizophrenia. One of them is a theory assuming a pathogenic role of infectious factors, among others,

retroviruses [3]. An evolutionary theory of schizophrenia proposed by Crow assumes that schizophrenia is a result of disturbances in the evolution of language, also in the context of abnormal interhemispheric communication and changes within the chromosomes X and Y [4]. This Crow's idea was discussed within the framework of the evolutionary concepts of schizophrenia presented during my work at the Department of Adult Psychiatry, Poznan University of Medical Sciences, as an example of so-called non-adaptive hypothesis [5]. Timothy Crow also contested the dichotomic concept of psychiatric disturbances presented by Emil Kraepelin in 1899. Crow was an advocate of the continuum of psychiatric disturbances, spanning from unipolar mood disorder through bipolar and schizoaffective disorder, to schizophrenia, with a progressive degree of mental defect [6]. This eminent contemporary psychiatrist was the guest of the Polish Psychiatric Association Congress in Warsaw, in 2004.

In the USA, the advocate of the theory of positive and negative symptoms became Nancy Andreasen, working at the University of Iowa, the long-standing Editor-in-Chief of the *American Journal of Psychiatry* [7]. She was also the author of the first psychometric scales for the assessment of these symptoms such as *the Scale for the Assessment of Positive Symptoms* (SAPS) and *the Scale for the Assessment of Negative Symptoms* (SANS) [8, 9]. She preferred the SANS, noticing that the acronym makes the French word for a lack of something. Andreasen also became a great follower of the neurodevelopmental concept of schizophrenia, which will be discussed later [10].

Nancy Andreasen was a member of the delegation of American psychiatrists visiting Poland at the beginning of the 1990s, supporting transformational changes in our country. On this occasion, there was a scientific conference in Krakow as well as a celebratory meeting of Polish and American psychiatrists (in the Rostworowskis' residence in Rybna near Krakow). At the beginning of the 2000s, Nancy Andreasen wrote a book *Brave new brain. Conquering mental illness in the era of the genome*, the title of which draws upon the famous Aldous Huxley's book *Brave new world* [11]. In 2003, Andreasen's book became available to Polish readers as *Fascynujący mózg* [12]. In the book *Creative brain* published in 2005, Andreasen put forward a hypothesis about a connection between the predisposition to schizophrenia and mathematical genius. She mentions genius mathematicians with severe schizotypal traits such as Albert Einstein and Bertrand Russell, in the families of which there were cases of full-blown schizophrenia. The most contemporary example in this respect is John Nash, Nobel laureate, the main character of the book and movie *A beautiful mind* [13].

The 1980s mark the beginning of the neurodevelopmental concept of schizophrenia. This theory assumes that in patients with schizophrenia, a genetic predisposition together with brain disturbances resulting from various factors, occurring in the prenatal, perinatal and early period of life, make the brain more vulnerable to the stressors occurring during adolescence and early adulthood. This leads to the development of the first psychotic episode. The hypothesis was independently formulated in 1987 by a British psychiatrist, Robin Murray, working in the Maudsley Hospital in London [14], and an American psychiatrist, Daniel Weinberger, from the National Institutes of the

Mental Health in Bethesda, Maryland [15]. Weinberger graduated from the medical faculty at the University of Pennsylvania in Philadelphia, the university at which I was a Fogarty Fellow in 1976–1977. Both researchers were the guests of the Polish annual schizophrenia conference organized by Professor Marek Jarema's team. Daniel Weinberger took part in the conference on the 10th anniversary of the neurodevelopmental concept, in 1997, and Robin Murray, in the conference on the 20th anniversary, in 2007.

In recent decades, the elements of the neurodevelopmental concept of schizophrenia have been verified in many studies. In the area of molecular genetics, it can be assumed that the first significant confirmation of this hypothesis took place in 2002 when, in the study of the large population of Iceland, the association between predisposition to schizophrenia and the gene of neuregulin, the substance linked with brain development, was demonstrated [16]. In subsequent years, the association between schizophrenia and many genes determining brain development has been found, mostly genes associated with the glutamatergic system. Many of these genes were included in the list of selected genes in the most important molecular-genetic research of schizophrenia using the genome-wide association study (GWAS) approach, published in *Nature* in 2014. The study included 37 thousand of schizophrenia patients and 133 thousand of healthy persons, demonstrating the association between the predisposition to schizophrenia and the polymorphisms of 108 genes [17].

Many studies have been also performed investigating the effect of infectious factors occurring during pregnancy on the occurrence of schizophrenia. The greatest specialist in this topic is Alan Brown, a current professor of psychiatry and epidemiology at the University of Columbia in New York. In 1977, as a freshmen resident in psychiatry, after graduating from the Jefferson Medical College in Philadelphia, he worked together with me in a laboratory at the University of Pennsylvania. According to him, the unquestionable effect of infection in pregnancy on predisposition to schizophrenia was demonstrated for the influenza virus and for a microbe, *Toxoplasma gondii*. The data on the HSV-2 (Herpes Simplex Virus Type 2) is still controversial. A mechanism of brain damage is associated with excessive activation of the immune system, facilitated by genetic predisposition. In this context, the role of neuregulin and *DISC1* (Disrupted-in-Schizophrenia-1) genes was suggested [18],

In the 21st century, the effect of childhood trauma on the occurrence and course of psychiatric disturbances in adulthood became a subject of great scientific preoccupation. It inevitably comes to mind that the topic draws upon the concept of Sigmund Freud, developed a century ago, suggesting that childhood events play an important role in psychiatric disturbances in later life. The pioneering study, also pertaining to schizophrenia, was published in 1999. Israeli researchers showed that parental loss, mostly before 9 years of age, increases 3.8-fold the risk for schizophrenia. An interesting fact was that this study, *par excellence* of psychological nature, was published in *Molecular Psychiatry* journal [19]. A recent review made by German authors also points out possible neurobiological mechanisms by which childhood trauma leads to the increased risk of schizophrenia and less favorable course of the illness [20].

In recent two decades, the situations facilitating the initiation of the first psychotic episode have also been a subject of interest. They encompass, among others, such 'social' aspects as urbanization [21] and migration [22] as well as the use of psychoactive substances, including cannabinoids [23]. The common final pathway resulting from these factors is increased dopaminergic activity [24].

After more than 30 years from its initiation, the neurodevelopmental concept of schizophrenia is alive and well. This was also confirmed by its authors who, on the 30th anniversary of this theory, published the articles in the 6th issue, 2017, of *Schizophrenia Bulletin* journal. Daniel Weinberger focused on genetic and epigenetic factors. He pointed out to a role in the schizophrenia of microscopic chromosomal aberrations causing various repeating of the genome fragments, called the copy number variations (CNV). They are especially important for fetal development and, besides schizophrenia, occur in excessive numbers in such developmental disorders like autism, intellectual disability or epilepsy. Whereas, epigenetic disturbances such as excessive methylation of DNA, causing a modifications of gene expression without influencing the genome structure, resulting from the environmental factors, occur mostly in the early period of life [25]. On the other hand, Robin Murray focused on the environmental factors leading to the initiation of the first psychotic episode of schizophrenia, such as childhood trauma, stressful events of adolescence period, urbanization and migration, as well as using psychoactive substances. According to him, the neurodevelopmental hypothesis of schizophrenia could be better named as the developmental risk factor model of psychosis [26].

For nearly 70 years, the basic pharmacological treatment of schizophrenia consists of the administration of neuroleptic (antipsychotic) drugs. Their introduction in the early 1950s [27] was a "Copernican" breakthrough in psychiatry when it turned out that psychotic symptoms can be treated with pharmacological drugs. However, for more than the next decade, nobody had the slightest idea about the neurobiological mechanisms associated with it. It was not until 1963, when a psychopharmacologist from Gothenburg, Arvid Carlsson (1923–2018), demonstrated that these drugs act on the dopaminergic system of the brain [28]. This started a great promotion of dopamine as an independent neurotransmitter. Hitherto, dopamine had been regarded as precursor substance for noradrenaline. It has been assumed that the dopaminergic hyperactivity is linked with the development of psychosis, and the inhibition of dopaminergic system (blocking dopaminergic receptors D2) is the main mechanism of therapeutic action of antipsychotic drugs. The concept of the association between dopaminergic hyperactivity and psychotic symptoms is still valid. Also, nowadays there is no antipsychotic drug with a pharmacological mechanism not based on the action on dopaminergic receptors. For his research on the dopaminergic system in the context of psychiatric disturbances and antipsychotic drugs, Arvid Carlsson was awarded the Nobel Prize in 2000.

When the idea of positive and negative symptoms of schizophrenia became established, the dopaminergic theory of schizophrenia evolved into a 'bipolar' one. In such an assumption, dopaminergic hyperactivity in subcortical structures was associated

with the production of positive (psychotic) symptoms. On the other hand, dopaminergic hypoactivity in the prefrontal cortex was responsible for mental deficits and cognitive impairment. The bipolar hypothesis of the dopaminergic system disturbances has been experimentally validated since the 1990s, due to the development of sophisticated neuroimaging methods. E.g., in patients with an exacerbation of schizophrenia, increased amphetamine-induced release of dopamine in the striatum was demonstrated, which correlated with the severity of positive symptoms [29]. Recently, a deficit of dopamine release in the dorsolateral prefrontal cortex was observed, and its severity correlated with impairment of working memory [30]. Nowadays, as the specific mechanism of dopaminergic dysfunction in schizophrenia, increased presynaptic dopamine synthesis, which results in its excessive release, is suggested [31]. However, in the aforementioned genetic study, the gene of the dopaminergic receptor D2 was identified as one of 108 genes associated with a predisposition to schizophrenia [17].

In the mid-1990s, Olney and Farber [32] put forward a glutamatergic hypothesis of schizophrenia, postulating a decrease in the activity of the glutamatergic N-methyl-D-aspartate (NMDA) receptor in this illness [32]. Also, Arvid Carlsson became a follower of the role of glutamatergic deficit in the pathogenesis of schizophrenia [33]. In subsequent years, the glutamatergic concept has been confirmed in numerous molecular-genetic studies [34]. It was also a basis for therapeutic attempts, mainly the use of inhibitors of the glycine site, a part of the NMDA receptor, for augmentation of neuroleptic drugs in the treatment of negative symptoms [35]. However, for the treatment of schizophrenia, the importance of the research on the glutamatergic system has been infinitesimal, compared to the dopaminergic system.

Concomitantly with the development of the neurotransmitter concepts of schizophrenia pathogenesis, the attempts were made to identify a biochemical disturbance that could be helpful in laboratory diagnosis of this illness. The first such attempt was a recognition of the so-called pink spot in the urine of patients with schizophrenia, by chromatographic method. Chemically, it is a metabolite of mescaline, dimethoxyphenylethylamine (DMPEA), a methylated derivate of dopamine [36]. It was hypothesized that in patients with schizophrenia, psychomimetic substances, responsible for psychotic symptoms, are produced, which is not the case in healthy subjects. Five years later, in a paper published in the prestigious journal *Nature*, Norwegian researchers indicated that pink spot is a result of the metabolism of drugs received by patients with schizophrenia [37]. Also, researchers from the Institute of Psychiatry and Neurology, under the direction of Professor Stanisław Pużyński did not find diagnostic usefulness of the pink spot [38]. Nowadays, the pink spot is rather considered as a historical peculiarity.

The niacin test, proposed by David Horrobin (1939–2003), the eminent British neurobiologist, in 1980, can be recognized as the first diagnostic test for schizophrenia. This test consists of an oral intake of 250 mg of nicotinic acid. This usually causes a skin flushing reaction which is absent in a proportion of schizophrenia patients. Horrobin hypothesized that non-flushing phenomenon results from a deficit of pros-

taglandin E1 synthesis, also associated with disturbances of dopaminergic activity [39]. Further research showed a subgroup (about 1/3) of schizophrenia patients not displaying the flushing after niacin. In the 1990s, a version of the test was elaborated consisting in topical application of nicotinic acid and assessing skin reaction in this spot [40]. The concepts of clinical characteristics of non-flushing patients have appeared as well as biochemical mechanisms of this phenomenon. Recently, German researchers showed that an impaired reaction to niacin occurs in the first episode of schizophrenia, in the high-risk subjects [41]. The disturbances of membrane phospholipid metabolism, especially phospholipase A2 (PLA2), the main enzyme of this process, are considered an important mechanisms associated with the niacin test. Therefore, after 40 years following its introduction, the niacin test still keeps some diagnostic value.

David Horrobin was a great advocate of a pathogenic role of lipid acids and membrane phospholipids in schizophrenia. In 2001, he published a book *The madness of Adam & Eve: How schizophrenia shaped humanity*, where he presented a possible role of lipid acids in the processes of the evolution of the human brain and their disturbances which can be associated with schizophrenia [42]. It is an interesting fact that Horrobin was born in Bolton, in the same year as Norman Davies, the great historian of Europe and Poland.

Author's scientific contributions to the pathogenesis and diagnosis of schizophrenia

The initiation of my own studies on the pathogenesis of schizophrenia coincided with taking up the function of the Head of the Department of Psychiatry, Medical Academy in Bydgoszcz, in 1985. The studies had two contexts: positive vs. negative symptoms of schizophrenia as well as comparing disorders in schizophrenia with the neurobiological abnormalities observed in affective disorders. In 1995, I returned to Poznan to become the Head of the Department of Adult Psychiatry, Poznan University of Medical Sciences. It was when the studies on the neurobiology of schizophrenia were extended by two significant aspects. Firstly, the research started on cognitive functions and eye movement disturbances in collaboration with the Neuropsychological Unit, Medical Academy in Bydgoszcz, directed by Professor Alina Borkowska. Secondly, the molecular-genetic studies were initiated in 1999, on account of constituting the Psychiatric Genetic Unit at Poznan University of Medical Sciences, headed by Professor Joanna Hauser.

In the late 1980s, in the Department of Psychiatry, Medical Academy in Bydgoszcz, some studies were conducted on the possibility of using Rorschach's test in the diagnosis of schizophrenia [43, 44]. One of the main interpretations of this test was elaborated by the eminent psychologist from Poznan, Zygmunt Piotrowski (1904–1985). Initially, he had worked at the Department of Psychology, Adam Mickiewicz University in Poznan, and since 1930, in various centers in the USA. During my scientific fellowship

in Philadelphia, in 1977, I had an extensive talk with him on Rorschach's test. He was then the Professor at the Hahnemann University Hospital in Philadelphia.

At the Department of Psychiatry in Bydgoszcz, an attempt of the verification of the niacin test was made. The frequency of non-flushing after oral intake of nicotinic acid, 200 mg, was compared between 33 patients with schizophrenia and 18 patients with depression in the course of unipolar or bipolar disorder. Before the test, all patients had their drugs discontinued for 7 days. The phenomenon of non-flushing occurred in ¼ of patients with schizophrenia, and in none of the subjects with mood disorder [45]. For this study, published in 1991 in *Biological Psychiatry* journal, I received a scientific prize from the Ministry of Health. Twenty years later, at the Department of Adult Psychiatry, Poznan University of Medical Sciences, a comparative examination of 29 patients with schizophrenia and 30 healthy subjects, matched for sex and age, was performed. A tissue paper with a 0.001 M solution of methyl nicotinate was applied topically for 90 seconds. Patients with schizophrenia had nearly two-fold weaker skin reactions compared to healthy persons. Among schizophrenia patients, there were no differences related to gender, duration of illness and taking antipsychotic medications [46]. A study on the polymorphism of the phospholipase A2 (PLA2) gene, located at chromosome 1p36.13, coding the main enzyme of phospholipid metabolism can be considered as corresponding to the concept of the niacin test. It is supposed that abnormal activity of the PLA2 can be associated with a pathological result of the niacin test in schizophrenia. In the paper published in 2003, a significant association between the *PLA2* gene polymorphism and an endophenotypic marker of schizophrenia such as eye movement disturbances was demonstrated [47].

In the early 1990s, in the Department of Psychiatry in Bydgoszcz, many neurobiological studies on the pathogenesis of schizophrenia were carried out. The methods included the dexamethasone suppression test, analysis of transmembrane lithium transport, and measuring the activity of such enzymes as adenosinetriphosphatase (ATPase) and inositol monophosphatase, on the erythrocyte model. The results showed a distinctiveness of disturbances of these processes in patients with schizophrenia in relation to healthy subjects, however, compared to depression, there were both differences and similarities. In many instances, gender differences were observed [48–52].

In 1997, in *Psychiatria Polska*, I presented the state of the art concerning research on the etiopathogenesis of schizophrenia. The article was about a status of the neurodevelopmental theory of schizophrenia, on its 10th anniversary, about current views on the mechanisms of psychopathological symptoms and therapeutic promises associated with the introduction of the new generation of antipsychotic drugs [53].

During my work in Bydgoszcz, there has been a gradual increase of interest in cognitive dysfunctions in schizophrenia, which could be considered as a comeback to the Kraepelinian concept of *dementia praecox*. It has been recognized that these dysfunctions make the core symptoms of schizophrenia and can be used as an endophenotype for molecular-genetic studies. Also, eye movement disturbances have been proposed as such an endophenotype. In collaboration with the Neuropsychological Unit, Medi-

cal Academy in Bydgoszcz, much research was carried out on cognitive dysfunctions and eye movement disturbances in schizophrenia. In one study, these parameters were compared in 21 patients with schizophrenia, their 33 healthy and 7 ill parents, and in 20 healthy control subjects age – and sex-matched. In the parents (first-degree relatives), significant cognitive and eye movement disturbances were found, which allows to consider these disorders as an endophenotype of schizophrenia [54]. These cognitive and eye movement endophenotypes were investigated in many molecular-genetic studies, described later.

The activity of the Psychiatric Genetic Unit, Poznan University of Medical Sciences in the first decade of 21st century was dominated by research on the so-called candidate genes. Such studies investigated polymorphism frequency of a gene coding given substance or enzyme whose role in the pathogenesis of schizophrenia has been proposed based on the results of biochemical or psychopharmacological studies. In some of these studies, the cognitive or eye movement endophenotype was used. Other research had the case-control design, comparing patients with schizophrenia with healthy subjects. Some of the results of these studies were described for the first time in the world.

The molecular-genetic study using the eye movement disturbances endophenotype showed that the polymorphism Ser9Gly of dopamine receptor D3 gene, located on chromosome 3q13.31 is associated with the severity of eye movement disturbances in patients with schizophrenia and in healthy persons. For this study, published in 2001 in *Molecular Psychiatry* journal, I received, together with Professor Joanna Hauser, a scientific prize from the Ministry of Health [55]. Employing the eye movement endophenotype revealed its association with already mentioned polymorphism of the *PLA2* gene [47], with HLA antigens [56] as well as the *COMT* (catechol-O-methyltransferase) gene. In the latter, the association was found only for males with schizophrenia [57].

In some molecular-genetic studies, a cognitive endophenotype was defined by the results of the Wisconsin Card Sorting Test (WCST), measuring the function of the prefrontal cortex. Much research has been performed on the association of such endophenotype with dopaminergic receptor genes *DRD1*, *DRD2*, *DRD3*, *DRD4*, and the genes of catecholamine inactivation such as *COMT*, *DAT* (dopamine transporter gene) and *NET* (noradrenaline transporter gene) [58, 59]. The most important achievement, for the first time described in psychiatric literature, was a demonstration of the association between the results of this test with the polymorphism of the *DRD1* receptor gene. The activity of dopaminergic receptor D1 significantly defines the efficiency of prefrontal cortex-related cognitive functions.

Tyrosine kinase *FYN* is associated with the activity of the glutamatergic receptor NMDA. In the association study with the WCST, the relationship between the *FYN* gene polymorphism and the cognitive performance of the prefrontal cortex was demonstrated. This may confirm the role of the glutamatergic system in cognitive functions [60].

Inspired by Professor Leszek Kaczmarek from the Nencki Institute in Warsaw, we began research on the matrix metalloproteinase (*MMP-9*) gene in psychiatric illnesses.

MMP-9 plays an important role in brain development and neuroplasticity, and in the context of the neurodevelopmental theory of schizophrenia, could have a relevant pathogenic significance. In a case-control study covering 442 patients with schizophrenia and 558 healthy persons, the team from Poznan demonstrated the association of the 1562C/T polymorphism of the *MMP-9* gene located on chromosome 20q13.12 with schizophrenia, for the first time in the world [61].

At the beginning of the 2000s, as the only representative of Poland, I joined the international consortium EGRIS (European Group for the Research of Schizophrenia). In 2002–2006, I was the national coordinator of the European First-Episode Schizophrenia Trial (EUFEST). In the EUFEST project, the efficacy of atypical antipsychotic drugs (amisulpride, quetiapine, olanzapine, ziprasidone) and low doses of haloperidol were compared in patients with the first episode of schizophrenia. Thirteen European countries plus Israel, including four Polish centers (Lublin, Lodz, Poznan, Warsaw) participated in the project. In Poland, 94 patients were recruited out of total of 498 participants (19.3%). The results of the EUFEST will be presented in the article on psychopharmacology.

For schizophrenia pathogenesis, an interesting observation of the EUFEST study was revealing an increased serum concentration of prolactin in patients with the first episode of schizophrenia, including those who were drug-naïve for antipsychotic treatment [62]. Hitherto, the role of prolactin in schizophrenia has been considered mainly in the context of hyperprolactinemia caused by an antidopaminergic effect of antipsychotic drugs. However, there is a possibility that prolactin can play a pathogenic role in the initiation of schizophrenia, independently of using antipsychotic drugs. The prolactin gene is located on chromosome 6p21, and the association of this locus with schizophrenia was found in many studies. In a case-control study covering 403 patients with schizophrenia and 653 healthy persons, the team from Poznan demonstrated the association of the functional – 1149G/T polymorphism of prolactin gene with schizophrenia, for the first time in the world [63].

As a member of the EGRIS group, I participated in the implementation of the new scales for the assessment of negative symptoms of schizophrenia. In 2018, in *Psychiatria Polska*, the current status of knowledge on the clinical picture, pathogenesis and psychometric assessment of these symptoms was presented [64]. Following the recommendation of American experts in 2006, the new scales for the assessment of negative symptoms have been elaborated, both clinical as well as self-assessment scales. In the Department of Adult Psychiatry, Poznan University of Medical Sciences, the Polish versions of the *Brief Negative Symptom Scale* (BNSS) [65] and *Self-evaluation of Negative Symptoms* (SNS) were created and verified [66].

In 2019, the 120th anniversary of the fundamental concept for the division of mental disorders, formulated by Emil Kraepelin, was observed. In *Current Psychiatry Reports*, I made an attempt to evaluate its current scene nowadays [67]. In a clinical sense, Kraepelin's dichotomic idea was undermined as early as in 1933, when Jacob Kasanin introduced the term schizoaffective psychosis [68]. After more than 50 years from this event, Timothy Crow placed this psychosis in the middle of the proposed

continuum of psychiatric disorders [6]. On neurobiological ground, a significant challenge of Kraepelin's division took place in the 1990s, when it was found that there is a remarkable overlap of genes predisposing to schizophrenia and bipolar disorder and that atypical antipsychotic drugs are therapeutically effective in both these illnesses. In the article, I focused mainly on showing a neurobiological distinctiveness of schizophrenia compared with bipolar disorder in many areas, especially in the context of the neurodevelopmental theory. The evidence has been accumulated showing the patients with schizophrenia are affected by more factors impeding brain development and are particularly susceptible to them. In the genome of schizophrenia subjects, there are more CNV changes, and infectious factors occurring during pregnancy, perinatal traumas, some social situations, as well as psychoactive substance abuse are more influential in this illness. According to some authors, the latter make the so-called second hit superimposing on the genetic predisposition. As a result, patients with schizophrenia during the first psychotic episode present more intensified neuroanatomical changes and cognitive disturbances compared to patients with bipolar disorder.

How the half-century of what has been going on in the pathogenesis of schizophrenia can be summarized? It seems that distinguishing specific schizophrenic symptoms (especially positive and negative) has allowed for a better description of the clinical picture and the targets for therapeutic impact. The neurodevelopmental theory of schizophrenia, assuming the interaction of numerous genetic and environmental factors remains impregnable. In the context of neurotransmitter-related treatment, the dominant has been the dopaminergic system, although, in many aspects, a significant role of the glutamatergic system has been demonstrated. It was accurately summarized in the title of an article with Arvid Carlsson as a co-author: *Schizophrenia: from dopamine to glutamate and back* [69].

And how the half-century of my own contribution to the research on the pathogenesis of schizophrenia can be summarized? As I pointed out in this article, I have attempted to make a small contribution to the scientific mainstream of the neurobiology of this illness. Whether I was successful, I leave this to the judgment of the readers.

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