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Bleuler and the Neurobiology of Schizophrenia

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Schizophrenia remains a major challenge for psychiatry. One hundred years after the publication of Eugen Bleuler's monograph, we are still debating the nosology and mechanisms of schizophrenia. We have stalled in the development of more effective treatments, after success with the introduction of antipsychotic medication. Cure and prevention remain in the distance. This article reviews the importance of Bleuler's monograph for the neuroscientific exploration of schizophrenia. While Bleuler assumed that schizophrenia has a neural basis, he remained agnostic on possible mechanisms and skeptical about the value of pathological diagnosis. He preferred psychological understanding over neural explanation. He gave hope by making schizophrenia dimensional and less predictive of course and outcome. To make progress now, we need to redefine schizophrenia at the level of the brain.

Key words: schizophrenia/history/neurobiology

At the dawn of the 20th century, the natural sciences were progressing rapidly. Physicists and biologists shifted paradigms with new theories of relativity and evolution. Physicians discovered microorganisms and developed life-saving vaccines and antibiotics. In contrast to this remarkable progress in the natural sciences, psychiatry was struggling to establish itself.

Since the enlightenment period, alienists had been taking care of the mentally ill in out-of-the-way mental asylums. The pioneers of academic psychiatry wanted to change this, but there was no established method for psychiatry as a natural science.[1] Clinical researchers proposed that psychiatric illnesses are discrete entities, just like other medical conditions. This was rejected by neuroscientists, who demanded a nosology grounded in human neuroanatomy.[2] A minority doubted either approach to mental illness and preferred to explore unconscious processes in the human mind.[3]

Bleuler's schizophrenia concept emerged in the midst of this debate. To capture the intellectual climate in European psychiatry around 1900, I will briefly review the contributions by 3 of his contemporaries: Emil Kraepelin, Carl Wernicke, and Sigmund Freud. The debate illustrates that the scientific status, of psychiatry in general and schizophrenia in particular, was never firmly established, anticipating the current request to rethink schizophrenia.[4]

Schizophrenia Before Bleuler

Emil Kraepelin (1850–1929) reshaped the largely descriptive discipline of psychiatry. Before him, arbitrary permutations of psychiatric signs and symptoms led to endless nosological disputes. For the first 20 years of his academic career, Kraepelin went along. But with the 5th edition of his textbook, published in 1896, he introduced a major change.[5] Without much, if any, data to back up his claim, he proposed that psychiatric disorders are "natural disease units" (natürliche Krankheitseinheiten). Simply put, he asserted that psychiatric disorders exist in nature and can be studied in the laboratory.[6] This fueled his research efforts and led to the creation of the first research institute dedicated to psychiatric disorders.[7] The greatest success story of this era was Alois Alzheimer's discovery of plaques and tangles in the brain of a demented woman.

Dementia praecox was Kraepelin's first and most cherished example of the natural disease unit concept. He continuously elaborated on the details of dementia praecox: clinical subtypes grew from 3 to 9; microphotographs were added to document emerging evidence of cellular pathology; genetic and environmental causes were explored. After his retirement, however, he began to question the ability of clinicians to accurately assign patients to the natural disease units he had created.[8] Especially the distinction of manic-depressive illness and dementia praecox, based on course and outcome, became doubtful, in no small part due to the acceptance of Bleuler's schizophrenia concept. But Kraepelin never questioned his concept of the natural disease unit. It has remained the foundation for our psychiatric research today, as we use categorical diagnoses to study the genetics, neural basis, and treatment of psychiatric disorders.[9] We still live in a Kraepelinian world.[10]

Carl Wernicke (1848–1905) spent much of his career discovering neural networks governing human behavior. His academic position gave him access to neurological and psychiatric patients and he complemented his clinical work with studies of human neuroanatomy. Like several other leading psychiatrists of his time (von Gudden, Flechsig, and Meynert), he was a neuroanatomist first, a clinician second.

Today Wernicke is recognized for the discovery of neural circuits that explain aphasia. In his lectures to medical students, he employed the same neural network approach to elucidate human behavior and psychiatric disorders. The transcripts of these lectures were published as ''Outline of Psychiatry'' (Grundriss der Psychiatrie).[11] The book was never translated into English, but a distillation of his major ideas was recently published.[12]

Wernicke was critical of Kraepelin's concept of psychiatric disorders as natural disease units. He did not believe that separate routes of investigation (ie, clinical observation, neuroscience, epidemiology) would converge toward valid disease entities. He asked for a radical paradigm shift: replace psychiatric nosology with a clinical neuroscience that is anchored in our understanding of human brain structure and function.[13] The psychiatrists who followed his lead, the Wernicke-Kleist-Leonhard school, remained a minority in academic psychiatry.[14] But Wernicke's scientific project anticipated much of the current discontent with psychiatric nosology.[15] The recent efforts of the National Institute of Mental Health to redefine psychiatric nosology with Research Domain Criteria are a revival of Wernicke's ideas.[16] Had he not died unexpectedly in 1905, psychiatry might have developed differently.

Sigmund Freud (1856–1939) pursued yet another, third path in psychiatry.[3] He abandoned his academic career as a neurologist and went into private practice in Vienna, exploring new therapeutic techniques to treat neuroses. While Kraepelin and Wernicke saw primarily asylum and hospital patients, Freud treated mainly affluent outpatients.

Many academic psychiatrists, including Kraepelin, were critical of Freud's work. Bleuler's department in Zuerich, however, was more receptive to the ideas of Freud and also of Janet, Freud's counterpart in France.[17,18] An important effort was Carl Jung's ''On the psychology of dementia. An attempt.'' (Über die Psychologie der dementia praecox. Ein Versuch).[19] Jung applied the emerging concepts of dynamic psychiatry to the explanation of abnormal thought processes in dementia praecox. He used association experiments, which were instrumental in establishing scientific support for psychoanalysis within academic psychiatry.[3]

Freud himself had little interest in psychotic disorders. But in 1911, the year of Bleuler's monograph, he published his analysis of the Schreber case, based on his reading of Schreber's autobiography.[20,21] His attempt, to explain paranoia as an unresolved conflict of homosexuality, did not gain much traction and Bleuler soundly rejected Freud's analysis in his 1912 review.[17,22,23]

How did Bleuler respond to the paradigms established before him? He embraced many of Kraepelin's clinical observations and accepted the notion that mental illness has a neural basis. But he agreed with Freud, Jung, and Janet, that the understanding of schizophrenia requires the study of unconscious psychological processes.

The Monograph in Bleuler's Life

Eugen Bleuler was 53 years old and at the height of his professional career when he published his schizophrenia monograph. He was born in 1857, 1 year after Kraepelin and Freud. When Bleuler was 17 years old, his older sister Paulina became mentally ill and was admitted to the nearby Burghoelzli hospital. The experience of having a mentally ill sibling contributed to Bleuler's decision to study medicine (the first in his family) and then pursue psychiatry.[24]

At the age of 29, Eugen Bleuler was appointed as the clinical director of the Rheinau clinic. For the next 13 years, he participated in the life of his patients, sharing regular meals, and working with them on the asylum grounds. Much of the case material in the schizophrenia monograph was collected during the time in Rheinau. While Bleuler was always interested in the unique biographies of his patients, Kraepelin derived his nosological insights from cards (Zaehlkarten), from which he extracted predictors of course and outcome. In 1898, Bleuler was appointed to the most prominent position of academic psychiatry in Switzerland, as Chair of Psychiatry at the University of Zuerich, and he became the director of the Burghoelzli. He moved with his family to the Burghoelzli, including his mentally ill sister.

Bleuler took over the Zuerich chair from Auguste Forel, who developed novel techniques to study human brain tissue and was a cofounder of the neuron theory. Forel, like many leaders of academic psychiatry in Europe at that time, was a neuroscientist. Bleuler had no training in neuroscience research, and he was not an experimentalist. While he was firmly grounded in the natural sciences, he recognized the limits of neuroscience in understanding the human mind. Jakob Klaesi, who trained and then worked with Bleuler at the Burghoelzli, wrote that Bleuler was ''never completely unified and, above all, never fully done (nie ganz einheitlich und vor allem nie wirklich fertig).''[25]

His reluctance to embrace experimental approaches might have contributed to his break with Carl Jung. When Jung asked for support to start a neuropsychological laboratory at the Burghoelzli, Bleuler did not support him as much as Jung had hoped. This led to Jung's resignation in 1909.[26] But Jung had already shaped Bleuler's thinking about psychotic disorders with his association experiments.

Bleuler developed the main ideas for his 1911 monograph over the course of several years. In "Affectivity, Suggestibility, and Paranoia" (Affektivität, Suggestibilität, und Paranoia), published in 1906, he developed some of the core concepts that later gave rise to 3 of the 4 fundamental symptoms (affectivity, ambivalence, and autism).[27] In the same year, he reviewed how the symptoms of psychosis could be interpreted as a result of neurotic conflicts.[28] Then, in 1907, Jung published "On the psychology of dementia praecox"[19] which Bleuler cited frequently in his monograph.

In 1908, Bleuler delivered a lecture at a scientific meeting in Berlin and proposed, for the first time, the term schizophrenia.[29] Interestingly, he suggested that the word schizophrenia is superior to dementia praecox because it can give rise to an adjective, eg, the "schizophrenic" patient. Since then, this linguistic "advantage" has turned into a liability.[30]

After the publication of the monograph, Bleuler continued to explain and defend his schizophrenia concept. In 1914, he responded to the early critics,[31] and at the end of his career, in 1930, he published a final review, with a focus on his distinction of primary and secondary symptoms.[32]

The Monograph

The 1911 monograph shaped the neuroscientific exploration of psychotic disorders in several ways. Most importantly, Bleuler preferred psychological understanding over neural explanation. Kraepelin's optimistic research agenda, ie, that we can study dementia praecox with the microscope, was replaced with a vague plan to unravel schizophrenia with the new concepts of dynamic psychiatry. This contributed to a noticeable slowing of basic neuroscience research in psychiatry. But with this turn, away from postmortem studies and toward a greater attention to biographical details, Bleuler laid the foundation for a less fatalistic view of course and outcome of psychotic disorders.

Bleuler did not define schizophrenia simply as a brain disorder. He assumed a physical disease process but considered it "not absolutely necessary."[33(p461)] The first study of cellular pathology in dementia praecox was published by Alzheimer in 1897.[34] While Kraepelin included photomicrographs of Alzheimer's work in his textbook, Bleuler did not mention these findings in his monograph. Even more, he proposed that the pathology of schizophrenia was not neuronal or cellular but one of connection or conduction: "The symptomatology of this disease differs basically from that of any other known organic or toxic disorder."[33(p462)]

Bleuler assumed that the psychological process of schizophrenia maps to a cerebral process, but he did not, like Wernicke, envision or propose any mapping. Based on Alzheimer's anatomical studies of dementia praecox, Kraepelin proposed that cellular pathology in the upper, but not lower, layers of the cerebral cortex gives rise to the clinical features of dementia praecox.[35] In his monograph, Bleuler remained completely silent on this topic. He considered the links between the anatomical findings and the clinical symptoms as forced and weak, stating that "anatomical findings do not correspond with the severity of the manifest symptoms."[33(p462)]

Bleuler used an example from clinical neurology to explain his neural model of schizophrenia: A lesion of the abducens muscle creates a paralysis of lateral eye movements (primary symptom) and a wrong localization of images (secondary symptom).[33(p348)] When applied to schizophrenia, this meant that the primary symptoms are close to the (unknown) neural substrate, whereas the secondary symptoms are more distant polymorph features of the illness. Bleuler proposed that the primary symptoms are caused by an organic illness, whereas the secondary symptoms are psychogenic and amenable to a dynamic (Freudian) interpretation. However, in contrast to his example from clinical neurology, Bleuler never elaborated on the equivalent of the abducens muscle lesion in schizophrenia. He left this for others to explore.

He devoted only 3 pages to the primary symptoms but more than 100 pages to an exploration of the secondary symptoms. He selects "disturbance of associations" as the main primary symptom and moves many other signs and symptoms (including affectivity, autism, and ambivalence) downstream from primary symptoms. The prominent position of association in Bleuler's epistemiology of schizophrenia is a result of his longstanding interest in association psychology and owes much to Jung's association experiments with schizophrenia patients.[36]

With his proposed gradient of an unknown disease process, giving rise to primary and then secondary symptoms, Bleuler pioneered a dimensional approach to psychotic disorders:

> … differentiation from the functional neuroses is so vague, that a mild schizophrenic may give the impression of a hysteric … Furthermore, practically all schizophrenic manifestations may appear to represent merely exaggerations of well-known neurotic symptoms.[33(p462)]

Finally, his distinction of fundamental symptoms (present in every case and during every period of the illness) and accessory symptoms (lacking during certain periods or completely) allowed for a more nuanced characterization of lifetime and episodic psychopathology.

The plural "schizophrenias" in the title of the monograph readily conveyed Bleuler's view that the illness was a constellation of various clinical presentations. He did not challenge Kraepelin's merging of hebephrenia, catatonia, and dementia paranoides into one diagnosis. But he rejected the notion of unity, which was at the center of Kraepelin's disease concept. Throughout his career, Bleuler remained more interested in the biography of his patients rather than a common neural mechanism.

Bleuler's Legacy

Bleuler's rejection of the name dementia praecox is often considered the most important contribution of his 1911 monograph. But the new name schizophrenia was the consequence of a more fundamental redefinition of schizophrenia as a psychological process rather than a fixed brain lesion.

By separating schizophrenia from degenerative illnesses with poor outcome, Bleuler provided the framework for the neurodevelopmental hypothesis and the stress-diathesis hypothesis. He also articulated the concern that the mapping of mental abnormalities onto brain circuits would not be trivial. Some of the current enthusiasm for neuroimaging as a major research tool in the study of schizophrenia is driven by the same concern—that schizophrenia cannot be mapped using cellular neuroanatomy.[37,38]

Bleuler's focus on the individual history of each patient influenced Adolf Meyer and through him generations of American psychiatrists.[39] Several prominent German psychiatrists did not endorse Kraepelin's natural disease units, but focused on psychopathology[40] and a pure psychiatry (ie, psychiatry without neuroscience), as articulated by Kurt Schneider and the Heidelberg school.[41] After the emigration of several German psychiatrists, especially Wilhelm Mayer-Gross, to England, the Heidelberg school and Bleuler influenced generations of British psychiatrists.[42] Finally, Bleuler's son Manfred contributed to schizophrenia research with his groundbreaking follow-up studies.[43]

While we have adapted Bleuler's term schizophrenia, most contemporary schizophrenia research is still firmly in the Kraepelinian tradition.[44] According to Berrios, schizophrenia research can be described as a set of research programs running in parallel, each based on different concepts of disease, mental symptom, and human mind.[45]

How can we make progress? We need to agree on shared observations, the generation of competing hypotheses and their subsequent "pruning" with experimental approaches.[46] While Bleuler did not doubt the neural basis of schizophrenia, he did not propose a neuroscientific research strategy. His ambivalence (Do we need to study the brain or the psychological conflicts of the person with schizophrenia?) is holding us back even today. We need to map the dimensional assessment of behavioral domains and mental states, well established in psychology, to the brain. Such a form of behavioral neurology (or biological psychology) is necessary to make progress in schizophrenia research.[47,48]

Bleuler was guided by his clinical observations and an attention to the unique story of each patient. He gave hope by making the diagnosis more dimensional and less predictive of course and outcome. But he did not create a vision for how we will uncover the neural basis of schizophrenia. This is our task now.

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