Diagnosis and Conceptualization of Mental Illness

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Abstract/key words

This chapter outlines the evolution of psychiatric understanding of mental disorders utilizing seven landmark texts that have informed current nosology. Important themes reviewed in this chapter include the foundational distinction between dementia praecox and manic-depressive insanity (Emil Kraepelin), drastic diagnostic differences between American and British psychiatrists reported in the 1970s (the US-UK diagnostic project), development of operationalized diagnostic criteria (Feighner criteria), the biopsychosocial model (George Engel), the philosophical account of mental disorder as harmful dysfunction (Jerome Wakefield), the endophenotype concept (Gottesman and Gould), and the Research Domain Criteria (RDoC) by National Institute of Mental Health. Historical and theoretical links between these different texts and thinkers are highlighted and are offered to the reader in an integrated narrative of psychiatry's conceptual development.

Key words: Psychiatric diagnosis; mental disorder; Emil Kraepelin; US-UK diagnostic project; Feighner criteria; biopsychosocial model; harmful dysfunction; endophenotype; Research Domain Criteria; RDoC

1.0 Introduction

This chapter charts the evolution of the conceptualization of mental disorders. We have selected seven landmark papers that have informed our current nosology; these texts also reflect the history of paradigm shifts within psychiatry. We begin with the 8th edition of Emil Kraepelin's famous textbook *Psychiatrie*, in which we find a mature version of his foundational distinction between *dementia praecox* and manic-depressive insanity; Kraepelin is widely acknowledged as having proposed the first systematized nosology in psychiatry based on a detailed understanding of clinical picture and longitudinal course. In the late 19th and early 20th century, the principal means of conveying new ideas in psychiatry was through textbooks rather than articles, and the selection of a volume of Kraepelin's textbook in lieu of a paper represents that historical reality. We then jump to Kendell and colleagues' classic 1971 paper from the US-UK diagnostic project, which reported drastic differences in the clinical application of diagnostic descriptions between American and British psychiatrists, particularly regarding schizophrenia. The poor reliability among experts on the two sides of the Atlantic raised serious concerns about

the integrity of the diagnostic process and served as a powerful wake-up call for the field. In response to this crisis, operational criteria were developed in an attempt to improve both reliability and validity. Building on Eli Robins and Samuel Guze's criteria for diagnostic validity, the paper by John Feighner and colleagues in 1972 represented the first systematic application of operational criteria for clinical diagnosis in psychiatry. Feighner's approach was eventually taken up and expanded by Robert Spitzer and colleagues to form the Research Diagnostic Criteria. The Research Diagnostic Criteria in turn became the backbone for the revolutionary third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) in 1980, which adopted operationalized diagnostic criteria for the first time, in the contrast to the first and second editions, which had relied on vague descriptions of disorders often based on psychodynamically driven etiological theories.

Operationalized criteria relied heavily on the "medical model" and dovetailed well with the growing "biological psychiatry" movement. This movement gained steam following the discovery of effective psychotropics in the 1950s, and subsequent decades saw a growing rift between "biological psychiatry" and "psychodynamic psychiatry." George Engel addressed the ongoing tension between psychological/psychodynamic theory and the medical model by proposing a biopsychosocial model, which provided a practical, but perhaps temporary, solution aimed at uniting the diverse camps within psychiatry. The discussion on the biopsychosocial model is represented here by Engel's 1977 paper in *Science*. Jerome Wakefield's highly influential philosophical account of mental disorder as harmful dysfunction is addressed next. This account, albeit not without philosophical limitations, helped reframe the conceptual debate by reintroducing concepts of disease mechanisms and their relationship to the appearance of psychiatric disorders. Finally, the last pair of articles highlight the endophenotype concept, proposed by Irving Gottesman, and the Research Domain Criteria (RDoC), proposed by Tom Insel, which seek to unite clinical diagnosis with an understanding of etiologic and pathogenetic mechanisms. These articles also reflect an ongoing paradigm shift in psychiatry, the fruits of which are yet to be seen. The RDoC framework, if successful in linking underlying neurobiological mechanisms to clinical syndromes, could fundamentally alter the way we think about psychiatric diagnosis and classification.

1.1 Kraepelin and the Foundations of Modern Clinical Nosology

Main Citation

Kraepelin, E. 1913. Psychiatrie. 8th edition, volume III. Leipzig: Barth.

English Translations of Relevant Chapters

Kraepelin E: Dementia praecox and Paraphrenia, Barclay RM (trans). E & S Livingstone. Edinburgh, 1919

Kraepelin E: Manic-Depressive Insanity and Paranoia, Barclay RM (trans). E & S Livingstone. Edinburgh, 1921

Background

The German psychiatrist Emil Kraepelin (1856 – 1926) is a towering figure in the history of psychiatry. His classification of mental disorders provides a foundation for modern psychiatric nosology, and post-psychoanalytic 20th century psychiatrists were proud to be a part of the self-identified "neo-Kraepelinian revolution" (1). Kraepelin presented his grand psychiatric framework in a series of editions of textbooks. These textbooks began to attract widespread attention with the 4th edition in 1893. The 8th and final edition was published in five volumes between 1909 and 1915. Edward Shorter states that editions of his textbooks were "anticipated with the same rapt attention that awaits new editions of the DSM today."(2)

Kraepelin is most well-known for his dichotomy of endogenous psychoses – i.e. the separation of "*dementia praecox*" (schizophrenia) from manic-depressive insanity (psychotic mood disorders), first proposed in the sixth edition of 1899; he justified this classification using commonalities and differences in clinical picture, course, and outcomes. Prior to Kraepelin, chronic illnesses with delusions, hallucinations, thought disorder, inappropriate affect, and social isolation did not exist as a unified category and were not differentiated from affective disorders. Benedict Morel had coined the term '*dementia praecox*' in French ('demence precoce') in 1852 to describe young patients with premature dementia. German psychiatrists Ewald Hecker and Karl Ludwig Kahlbaum had used the terms 'hebephrenia' and 'paraphrenia hebetica' respectively for a disease of younger patients manifesting florid psychosis and a deteriorating course. Kraeplin borrowed from Kahlbaum and developed these ideas further (3, 4). German psychiatry, prior to Kraepelin, had not systematically based the classification of mental disorders using course and outcomes as critical defining features (5).

The term '*dementia praecox*' first appears in Kraepelin's textbook in the 4th edition (1893) under the group heading of 'psychic degenerative processes'. It became an independent disease in the 5th edition. The 6th edition marked his greatest nosological contribution with two distinct, broad categories of disorder, i.e., *dementia praecox* and manic-depressive insanity. He included Kahlbaum's catatonia, Hecker's hebephrenia, and paranoia in his description of *dementia praecox*, and in the 7th edition, these appear as the hebephrenic, catatonic, and paranoid subtypes of *dementia praecox*. In the 8th edition, Kraepelin recognized that some cases of *dementia praecox* may have a late onset and that a few cases may recover.

Method

Kraepelin was an astute and experienced psychiatric clinician. He aimed to accurately describe and classify psychiatric symptoms, in contrast to other psychiatric researchers of his era who were occupied with neuroanatomical and neuropathological research and paid little attention to nuances of clinical presentation and course.

Kraepelin's work was based on detailed clinical observation and case notes of thousands of patients; it is estimated that he cared for over 8000 patients in Munich and Heidelberg (4). Kraeplin believed in the necessity of systematic and objective observation of his patients. To accomplish that, he utilized 'diagnostic cards', which were developed for the purpose of record-keeping in psychiatric institutions. He kept records, among other things, of age, age of onset, family history, medical history, treatment and duration of treatment, clinical features, and course of symptoms (4).

Kraepelin utilized a validation schema that foreshadowed the one proposed by Robin and Guze later in the 20th century; he emphasized clinical presentation, features of course and outcomes, and family aggregation of disease as factors distinguishing different conditions. He also found premorbid personality and temperament to be useful for classification purposes.

Results

At the heart of Kraepelin's classification system is the division between *dementia praecox* and manic-depressive insanity. In his own words: "*Dementia praecox* consists of a series of states, the common characteristic of which is a peculiar destruction of the internal connections of the psychic personality. The effects of this injury predominate in the emotional and volitional spheres of mental life." (6) (p 3) "Manic-depressive insanity… includes on the one hand the whole domain of so called *periodic and circular insanity*, on the other hand *simple mania*, the greater part of the morbid states termed *melancholia* and also a not inconsiderable number of cases of *amentia*. Lastly, we include here certain slight and slightest colourings of *mood*, some of them periodic, some of them continously morbid, which on the one hand are to be regarded as the rudiment of more severe disorders, on the other hand pass over without sharp boundary into the domain of *personal predisposition*." (7) (p 1)

Kraepelin was convinced that each condition represented a distinct morbid process, despite variation in clinical presentations of *dementia praecox* and manic-depressive insanity. Kraepelin elaborated on various differences in past history, symptoms/signs, and course of illness to arrive at his differential diagnosis. *Dementia praecox* was in the majority of cases a chronic condition with poor prognosis, resulting in a state of "dementia", while manic-depressive insanity was more cyclical and had a relatively good prognosis. Episodes of manic-depressive insanity could be prolonged, but recovery was expected. The recovery between episodes wasn't always complete; recurrent attacks could lead to some residual impairment. Kraepelin was skeptical of the search for the pathognomonic symptom, and he always stressed the importance of considering the total clinical picture (8).

Kraepelin did not view *dementia praecox* as always chronic nor manic-depressive insanity as always remitting with complete recovery in between episodes. Kraepelin was aware that we cannot distinguish satisfactorily between these two illnesses based on clinical picture and course alone. However, he continued to assert that fundamentally different basic pathological processes underpinned these two conditions.

Conclusion/Critique

Kraeplin's methodology and classification have proven to be of lasting significance (1, 4, 8). His landmark contributions lie in utilizing disease course and outcomes as principles for classification and in distinguishing *dementia praecox* as a distinct entity from psychotic mood disorders.

Kraepelin's concept of *dementia praecox* is well-preserved in modern psychiatry in the construct of schizophrenia; his unitary notion of affective disorders, in comparison, has not been adopted by contemporary classifications. It is a common misconception that manic-depressive insanity corresponds to modern bipolar disorder. In fact, it includes the entire affective spectrum. Manic-depressive insanity, as conceptualized by Kraepelin, comprises the entire range of disorders with singular or recurrent episodes of both polarities. His views align with more modern dimensional concepts of mood disorders (9).

The recognition that many patients experience a "schizoaffective disorder" with features of both illnesses has raised the question from the very beginning of whether schizophrenia can be clinically categorized as a distinct entity from mood disorders. Recent genetic studies have also cast doubt on the notion that schizophrenia and bipolar disorder have distinct genetic underpinnings (10). Whether etiology-based classifications of the future will preserve the Kraepelinian distinction is an open question.

Kraepelin's emphasis on course and outcome as a critical defining features of psychiatric illnesses was revived in American psychiatry in the later-half of 20th century by Robins and Guze (see section 1.3). By and large, current diagnostic thinking, as exemplified by the DSM, remains neo-Kraepelinian in spirit.

1.2 Crisis of Reliability: the US-UK diagnostic project

Citation

Kendell RE, Cooper JE, Gourlay AJ, Copeland JR, Sharpe L, Gurland BJ. Diagnostic criteria of American and British psychiatrists. Arch Gen Psychiatry. 1971 Aug;25(2):123-30.

Background

Multiple studies from the first half of the 20th century suggested problematically poor interrater reliability for psychiatric diagnoses. For instance, in one study, three clinicians agreed on a psychiatric diagnosis only 20% of the time when seeing the same patient (11). The 1960s and early 1970s further highlighted this crisis of reliability with the discovery of stark differences in diagnostic practices between psychiatrists from the UK and US. Studies of hospital records had revealed that the diagnosis of schizophrenia in the inpatient setting was consistently more prevalent in America, while in Britain the diagnosis of manic depressive illness was more frequently used (12). In one study, American psychiatrists diagnosed depressive neurosis more readily as compared to British psychiatrists' preference for manic depressive illness (13). In another study, American psychiatrists provided a range of diagnoses of schizophrenia, neurosis,

and personality disorder after viewing a single diagnostic interview, while 60% of British psychiatrists diagnosed personality disorder and none diagnosed schizophrenia on watching the same interview (14). These findings prompted the creation of the Cross-National Project for the Study of the Diagnosis of Mental Disorders in the United States and the United Kingdom, which began as a series of studies in 1965. The project used semi-structured interviews, ratings of videotapes, and systematic examinations of case records and was carried out by multidisciplinary teams based in New York and London (12, 15). The Kendell paper is perhaps the most well-known of these, given the striking findings it reported from a well-designed experiment, and will be discussed here in detail.

Methodology

The study was conducted using videotapes of unstructured diagnostic interviews with eight patients, 20 to 50 minutes in duration. Given the audience, five of these patients were British and three were American. The investigators selected cases that included both classic presentations and presentations that would evoke dissent. Around 240 British psychiatrists and 450 American psychiatrists participated in rating the videos; the American sample was drawn predominantly from the New York Psychiatric Institute and other New York metropolitan area hospitals. A minimum of four years of psychiatry experience was required (average age of experience was 12-15 years). All clinical information was to be gleaned from the videos only; however, certain slang phrases and allusions were explained.

Participating psychiatrists were asked to provide three sets of ratings:

1) Lorr's Inpatient Multi-dimensional Psychiatric Scale (IMPS), which consists of ratings in non-technical language covering a variety of abnormal behaviors
2) Checklist of 116 technical terms to describe observed psychopathology (such as retardation, blocking, and flattening of affect)
3) Primary diagnosis (to be picked only from ICD-8 diagnoses), with provisions for a subsidiary diagnosis and an alternative diagnosis if needed. In addition, participants could also provide a "personal diagnosis" unrestricted by ICD-8 terminology. A 5-point confidence scale was attached to the main diagnosis, since the investigators thought that many psychiatrists might not be strongly confident about a diagnosis based on the limited information provided in the video.

Results:

Three out of these eight patients exhibited typical symptoms of classical diagnostic stereotypes (paranoid schizophrenia with the possibility of an alcoholic psychosis, depressive illness, and schizophrenic illness), and there was substantial agreement between the ratings of American and British psychiatrists for these videos. Three other patients showed a mixture of psychotic and affective symptoms. The proportion of British psychiatrists making a diagnosis of affective psychosis was higher compared to American psychiatrists. Despite this relative difference, the majority of psychiatrists on both sides arrived at the same diagnosis.

The most serious disagreement occurred with two cases, where the majority of American psychiatrists diagnosed some form of schizophrenia, while the majority of British psychiatrists diagnosed personality disorder or neurotic illness. Many American psychiatrists utilized the diagnosis of ‘pseudoneurotic schizophrenia’ (a now obsolete diagnostic category in which prominent symptoms of anxiety, obsessions, compulsions, and phobias were believed to mask a latent psychotic disorder) while this diagnosis was rarely utilized by British raters.

The study also revealed that American and British psychiatrists not only differed in the diagnosis given, but also in their detection of observed symptomatology. In the case of patient F, for example, 67% of American psychiatrists rated the patient as having delusions, 63% as having passivity feelings, and 58% as showing thought disorder. This is in contrast to British psychiatrists, whose ratings were respectively 12%, 8% and 5%. Even when using IMPS ratings, which are straightforward, non-technical descriptions, American psychiatrists were more likely to perceive symptomatology as having stronger schizophrenic connotations.

There were other differences as well; for instance, the British observed hysteria more commonly than Americans, and the Americans diagnosed involutional melancholia in middle-aged women, where British psychiatrists diagnosed manic depression. However, the differences in schizophrenia diagnosis were the starkest finding: many of the patients diagnosed with schizophrenia in New York would have been diagnosed with manic-depressive illness in London (12, 15).

Conclusion and Critique

The study demonstrated very clearly that the concept of schizophrenia in the US, at the very least among psychiatrists on the east coast, was broader than the British concept of schizophrenia. In the discussion of the paper, the authors noted that the diagnosis of schizophrenia, "is now made so freely on the east coast of the United States that it is losing much of its original meaning and is approaching the point at which it becomes a synonym for functional mental illness." (16) Seven of the eight patients in the study had been diagnosed as schizophrenic by over two thirds of American psychiatrists.

As stated above, the Kendell paper was part of the larger US-UK Project, which found that inconsistent diagnostic methods for routine hospital admissions in the two countries led to large discrepancies in diagnosis. These findings highlighted the crucial need for diagnostic reliability and prompted the development of operationalized diagnostic criteria. The problem of reliability also had implications for the validity of psychiatric diagnosis, since a lack of reliability precluded a lack of validity.

Another highly publicized, and much more theatrical, study from the early 70s, was the Rosenhan Experiment ('On being sane in insane places') (17). The study was conducted by David Rosenhan, a psychologist at Stanford, and highlighted problems with the overall reliability of

identifying individuals with mental illness. The experiment involved sending 8 healthy volunteers to different hospitals across US with feigned auditory hallucinations (voices saying the words “empty,” “hollow”, and “thud”) and no other psychiatric symptoms and no prior psychiatric history; all patients were admitted to psychiatric units. After admission, these patients acted as their normal selves and reported no further auditory hallucinations. Despite normal behavior on the unit, hospital staff viewed their behavior as reflective of a mental illness. All were given antipsychotic medications (which the “pseudopatients” did not swallow). Seven were diagnosed with schizophrenia and one with manic-depressive psychosis. The duration of admission ranged from 7 to 52 days. The biggest critique of this study is that it lacked realism – psychiatrists, and physicians in general, do not begin with the assumption that a patient is feigning symptoms. Nevertheless, the study highlighted the problem of reliability of the over-arching category of “mental disorder”, and further spurred the psychiatric community to place psychiatric diagnoses on a more solid footing.

1.3 The Development of Operationalized Criteria

Main Citation

Feighner JP, Robins E, Guze SB, Woodruff RA Jr, Winokur G, Munoz R. Diagnostic criteria for use in psychiatric research. Arch Gen Psychiatry. 1972 Jan;26(1):57-63.

Related References:

Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. Am J Psychiatry. 1970; 126: 983-987.

Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria: rationale and reliability. Arch Gen Psychiatry 1978; 35:773–782

Background

In the mid-20th century, American psychiatry displayed little interest in psychiatric diagnosis. The dominant framework of psychoanalysis emphasized individual differences rather than commonalities in presentation, with little use for the types of broad diagnostic labels used by other medical specialties. In the 1950s, when nearly every psychiatry department in the US was dominated by psychoanalytic theory and practice, the Department of Psychiatry at Washington University in St. Louis, Missouri was a prominent exception (18). Edwin Gildea, then Department Chair, believed in open-minded inquiry with respect to biological theories. With this support, a small group of psychiatrists in the department led by Eli Robins and Samuel Guze set out on the ambitious project of providing psychiatry with operationalized diagnostic criteria that were valid and reliable. Robins and Guze viewed psychiatry from the lens of the medical model, where diagnosis plays a central role. They outlined a five-phase diagnostic

validation model for psychiatric diagnosis (19). Their way of thinking with its emphasis on the clinical picture and longitudinal course was clearly neo-Kraepelinian in spirit.

Robins and Guze continued to promote this line of inquiry in their department with colleagues and trainees. In 1967, John Feighner, then a psychiatry resident, created a discussion group with Eli Robins as senior mentor, along with Samuel Guze, George Winokur, Robert Woodruff, and Rod Muñoz as active participants. They initially intended to write a literature review of key contributions to psychiatric diagnosis but ultimately claimed the more ambitious task of developing a set of operationalized diagnostic criteria for multiple mental disorders. These criteria were published in 1972 and are generally referred to as the 'Feighner criteria'. The criteria filled a much-needed void (DSM-I and DSM-II only contained brief and vague descriptions of mental disorders and were of little help in making the process of diagnosis reliable) and were quickly and widely adopted by clinicians and researchers, making this article one of the most cited publications in psychiatry.

Methodology

As mentioned above, Robins and Guze had earlier devised a strategy for validating a psychiatric diagnosis, based on the following five phases (19):

1. Clinical description: clinical description of the constellation of signs and symptoms associated with the condition, including items such as race, gender, age of onset and precipitating factors.
2. Laboratory studies: chemical, physiological, radiological, anatomical findings as well as findings from psychological testing
3. Delimitation from other disorders: exclusion criteria to exclude other disorders with similar clinical features
4. Follow-up studies: looking at diagnostic stability, longitudinal course, and treatment response. Marked difference in outcomes, such as between complete recovery and chronic illness, suggests that the group is not homogenous and challenges the validity of the original diagnosis
5. Family history: increased prevalence of same disorder among close relatives of original patients.

The Feighner criteria followed this framework and drew data from thorough literature review, clinical experience, and group discussion. The meetings continued for approximately 9 months, and Feighner gathered the materials for the literature review and developed working outlines of the diagnostic criteria. The other authors would meet, review Feighner's proposed criteria, revise them in light of their own knowledge, research and clinical experience, and finalize them based on consensus.

Results

The project resulted in operationalized diagnostic criteria for 15 psychiatric conditions: primary affective disorders (depression and mania) and secondary affective disorder (depression only), schizophrenia, anxiety neurosis, obsessive-compulsive neurosis, phobic neurosis, hysteria, antisocial personality disorder, alcoholism, drug dependence, mental retardation, organic brain

syndrome, homosexuality, transsexualism, and anorexia nervosa. The criteria also allowed clinicians to note that a patient had "undiagnosed psychiatric illness" when his/her symptoms did not fit under any other specific disorder (20).

For example, the Feighner criteria for depression (20) required:

- a dysphoric mood (including feeling "depressed, sad, blue, despondent, hopeless, 'down in the dumps,' irritable, fearful, worried, or discouraged")
- at least four additional symptoms for "probable" depression and at least five additional symptoms for "definite" depression; these symptoms can be "poor appetite or weight loss," "sleep difficulty," "loss of energy," "agitation or retardation", "loss of interest in usual activities, or decrease in sex drive", "feelings of self-reproach or guilt", "complaints of or actually diminished ability to think or concentrate", "recurrent thoughts of death suicide"
- a time duration of at least one month with "no preexisting psychiatric conditions." . The criteria specifically excluded "schizophrenia, anxiety neurosis, phobic neurosis, obsessive compulsive neurosis, hysteria, alcoholism, drug dependency, antisocial personality, homosexuality and other sexual deviations, mental retardation, or organic brain syndrome." They further specified that "patients with life-threatening or incapacitating medical illness preceding and paralleling the depression do not receive the diagnosis of primary depression."

Contemporary readers will notice the striking resemblance with the symptom profile for current DSM criteria for major depression, though the time duration has been shortened and the exclusion criterion has been lifted.

The reliability and validity of the criteria was established in an 18-month follow-up study of 314 psychiatric emergency room patients and a 7-year follow-up study of 87 psychiatric inpatients at Washington University in St. Louis. Reliability, as measured by inter-rater agreement about diagnosis, was 86-95% in the emergency room and 92% for inpatients. Validity, defined as the agreement between initial and follow-up diagnoses, was 93% and 92% respectively (20).

Conclusion and Critique

The influence and legacy of the Feighner criteria are manifold (18). First and foremost, the Feighner criteria represented the first systematic application of operationalized criteria for psychiatric diagnosis into psychiatric practice. Moreover, Feighner demonstrated that the approach could identify a broad array of disorders. Second, the success of the Feighner criteria forced American psychiatry to pay attention to the course and outcome of a clinical syndrome as critical defining features. This line of thinking had been a prominent feature of European descriptive psychiatry, exemplified by the work of Kraeplin, but had been lost to American psychiatry. Third, the Feighner criteria were a major milestone in a broader research program aimed at developing empirically validated psychiatric diagnoses. It is important to keep in mind

that the Feighner criteria were based on research findings whenever available, but that the available research data at that time was highly limited.

Another important way in which Feigner criteria shaped history is by serving as a forerunner to the development of the DSM-III via the development of the Research Diagnostic Criteria (RDC) (21). Robert Spitzer at Columbia along with psychologist Jean Endicott had been working on improving psychiatric diagnosis for many years. Their initial efforts came in the form of a computer algorithm called DIAGNO, which provided diagnoses based on raw clinical data entered by clinicians. DIAGNO was not easily adopted into research or clinical practice. After the publication of the Feighner criteria, Spitzer and Endicott collaborated with Eli Robins, one of the original authors of the Feighner criteria, to create an updated version known as RDC that laid out operationalized criteria for 25 major diagnostic categories (21).

While the Feighner group was primarily interested in improving the validity of psychiatric diagnosis, the Spitzer group was primarily interested in establishing reliability. The Spitzer group believed that variability in the criteria used for diagnosis was the biggest contributor to poor reliability among clinicians, and stressed the use of specific inclusion and exclusion criteria for each disorder as crucial to this endeavor. The Spitzer group were among the first to use the kappa coefficient statistic to measure diagnostic reliability while correcting for chance agreement (21).

Spitzer and Endicott believed that there were three major lessons from the Feighner group that influenced the development of RDC and subsequently the DSM-III: the use of operationalized criteria, paying attention to course of illness and prognosis in addition to acute clinical picture, and wherever possible, basing diagnostic criteria on research data rather than just clinical experience and consensus (18).

The RDC were developed to enable researchers to apply a consistent set of criteria for the description or selection of subjects with psychiatric disorders, and the final version of the RDC was published in 1978 (21). The reliability of the RDC was shown to be considerably better than psychiatric diagnoses otherwise determined. The success of the RDC paved the way for the inclusion of specified diagnostic criteria for more than 200 mental disorders in DSM-III. Spitzer later wrote that the inclusion of diagnostic criteria in DSM-III was only possible because RDC "tested the water, and clinicians and researchers saw the advantage of replacing vague descriptions of psychiatric disorders with precise definitions using specified criteria." (22)

1.4 The Biopsychosocial Revolution

Main Citation

Engel G. The need for a new medical model: a challenge for biomedicine. Science. 1977; 196: 129–136.

Related References:

Engel G. The clinical application of the biopsychosocial model. Am J Psychiatry. 1980; 137: 535–544.

Background

The biopsychosocial (BPS) model, proposed by George Engel, is now so commonplace in contemporary psychiatry as to be as axiomatic. It is a difficult to imagine a time when this was not the case. The BPS model represents both a philosophy of clinical care and a practical clinical guide. Biologically oriented research in the 1960s and 1970s led to a sharp increase in support for the medical model, which viewed disorders in more biological terms, and perhaps with the implicit inference that clinicians need not be concerned with psychosocial issues. This led to an increase in tension between psychoanalytically-minded and biologically-minded psychiatrists.

Methods**:**

Engel constructed the BPS model utilizing a basic framework provided by general systems theory. According to systems theory, nature is organized in the form of a hierarchically arranged continuum of systems (or levels of explanations), with more complex, larger units superordinate to the less complex, smaller units. Each system – such as cell, organ, person or family – is at a particular level of complexity, with its own distinctive qualities and relationships, requiring explanatory frameworks that are unique to that level. Each system is not merely an assemblage of its constituent parts, but also exists in relationship to other systems. Building on this theoretical foundation, Engel offered a framework that accounted for all systems relevant to the biological, psychological and social domains involved in mental illness.

Results:

Engel's purpose in writing these two classic papers is two-fold: firstly, to show the deficiencies of biomedical reductionism, and secondly, to propose the BPS model as the preferred alternative. The biomedical model, as Engel viewed it, assumed "disease to be fully accounted for by deviations from the norm of measurable biological (somatic) variables." (23) In other words, the biomedical model could conceptualize disorders as entities independent of social behavior.

Engel argued that biological abnormalities at best constitute a necessary but not sufficient condition for illness and, in particular, for the human experience of the disease. To take into account the human experience of disease – whether and when patients come to view themselves or be viewed by others as sick, how illness is reported, and how it impacts human lives – is impossible without considering psychological, social, and cultural factors (23, 24).

Establishing a relationship between a clinical presentation and an underlying biological etiology requires a scientific understanding of behavior and psychosocial aspects because that is how patients report their symptoms. Patients seek help from the clinician because either they do not know what is wrong or, if they do, they feel incapable of helping themselves. Engel argues

that the "psychobiological unity of man" requires that clinicians accept the responsibility to evaluate and manage whatever problems the patient presents, regardless of whether they can be reduced to biological disruptions in the body.

Engel recognized the unique position of psychiatry within the medical profession as the only clinical discipline still concerned primarily with the study of the human condition. He considered it a lasting contribution of Freud and Meyer that they had provided frames of reference which led to the inclusion of psychological processes in the concept of disease.

Engel maintains that the clinician must accurately determine the patient's experience of illness, formulate possible explanations for the clinical presentation, utilize further interviewing or laboratory studies to verify and reject hypotheses, and then determine a treatment plan in which the patient's cooperation is ensured. All these practical steps require a thorough understanding of psychological and social factors influencing the patient: "To provide a basis for understanding the determinants of disease and arriving at rational treatments and patterns of health care, a medical model must also take into account the patient, the social context in which he lives, and the complementary system devised by society to deal with the disruptive effects of illness, that is, the physician role and the health care system. This requires a biopsychosocial model." (23)

Conclusion and Critique

Engel conceptualized the biopsychosocial model as "a blueprint for research, a framework for teaching, and a design for action in the real world of health care." (23) Philosophically, it is a way of understanding how suffering and illness are affected by multiple levels of organization, from the social to the molecular. At a practical level, it is a way of understanding the patient's subjective experience as an essential contributor to accurate diagnosis, health outcomes, and humane care (25).

The BPS model has been of tremendous influence in psychiatry and psychology, and within a short period of time it achieved the status of psychiatric orthodoxy. It has at least partially resolved the debates between the psychodynamic and biological camps within psychiatry by offering a model acceptable to all parties. There is no doubt that the BPS model is an advance over earlier models. However, critics argue that in contemporary practice the biopsychosocial model has evolved into a confusing set of assumptions about the content of psychiatric conditions, leading the clinicians into a state of lazy eclecticism (26). As interpreted by most mental health professionals today, this model does little but assert that all illnesses have components that are, unsurprisingly, biological, psychological, and social (26).

Paul McHugh and Philip Slavney argue that the biopsychosocial model is excessively broad and provides no real guidance to clinicians or researchers. They compare the model to a list of ingredients, as opposed to a recipe. In their view, the BPS model only lists relevant aspects of psychiatry. It is silent as to how to understand those aspects under different conditions and in different circumstances (27).

Biopsychosocial thinking has evolved into a mature philosophy of psychiatric pluralism in recent years. The conceptual framework of pluralism in psychiatry originates from the work of early 20th century psychiatrist and philosopher Karl Jaspers, and has been elaborated by contemporary thinkers such as McHugh, S. Nassir Ghaemi and Kenneth Kendler. The basic viewpoint of pluralism is that multiple independent methods and levels of explanations are necessary to understand and treat mental illness. Pluralism explicitly recognizes the strengths and limits of each method or explanation, and recommends using whichever is best suited for the specific circumstances based on empirical evidence (26). Kendler advocates for an 'integrative pluralism' in which active efforts are made to incorporate divergent levels of analysis. For complex disorders, single-level analyses usually lead to partial answers; integrative pluralism seeks to establish small “local” integrations across levels of analysis (28). Pluralism is the natural successor to the BPS model and may very well supplant it in the future.

1.5 Mental Disorder as Harmful Dysfunction

Main Citation

Wakefield JC. The concept of mental disorder: on the boundary between biological facts and social values. Am Psychol. 1992; 47: 73–88.

Related References:

Wakefield JC. Disorder as harmful dysfunction: a conceptual critique of DSM-IIIR's definition of mental disorder. Psychol Rev. 1992; 99: 232–247.

Background

The concept of mental illness has been the subject of heated debate for several decades, particularly as psychiatry has been routinely charged with addressing normal suffering or problems of living. Philosophically, disease concepts can involve normative, value-based judgments or scientific, fact-based judgments. Value-based judgements include matters such as social deviance, moral disapproval, and considerations of harm, while fact-based judgements include notions of statistical deviation, biological disadvantage with regards to fertility or mortality, and presence of biological pathology. This basic division is at the heart of the dispute, with the debate often being framed in terms of whether the identification of an individual as disordered is sociopolitical or biomedical. Philosophers such as Michel Foucault, and psychiatrists such as Thomas Szasz and R.D. Laing were of the position that psychiatric diagnoses were masked sociopolitical judgements (a position embraced by the antipsychiatry movement), while commentators such as John G. Scadding, Robert Kendell and Christopher Boorse were in the biomedical camp.

Thomas Szasz created intense controversy in the field with his 1960 article and book *The Myth of Mental Illness*, in which he began by defining disease as demonstrable anatomical or

physiological lesions. This definition implies that the only sort of disease that can exist is physical; since disease cannot be non-physical. In other words, the "mind" cannot be diseased in the literal, physical sense since it is non-physical. His conclusion was that mental disorders can therefore only be diseases in a metaphorical sense. If psychiatric symptoms are due to a neurological defect, then these conditions are brain diseases, and if psychiatric symptoms are not due to a brain disease, then they are only non-pathological problems in living. In either case, Szasz argues, the concept of mental illness is unnecessary and misleading (29).

Jerome Wakefield defined disorder (including mental disorder) as 'harmful dysfunction' and maintained that the concept of disorder must include a factual component so that disorders can be distinguished from disvalued conditions. At the same time observable facts alone are not enough, and disorder also requires harm, which involves values. By this hybrid account, Wakefield suggested a unifying and appealing ground that has understandably been of great influence.

Wakefield agrees with Szasz that disorder requires physical abnormality but doesn't accept Szasz's argument or conclusion. Wakefield sees the notion of "lesion" as too narrow and inapplicable to many conditions in medicine. Furthermore, Wakefield doesn't conceptualize mental disorders as disorders of the non-physical "mind", but rather as disorders of "mental functions" in the brain. Thus, the same concept of disorder can apply to physical as well as mental disorders.

Methods

Wakefield conducts a conceptual analysis of the concept of disorder. He recognizes that we value many conditions negatively, but that our notion of disorder is not reduced to the notion of merely a disvalued condition. Our notion of disorder also seems to make inherent reference to abnormality or malfunction in some biomedical processes. Based on his analysis, Wakefield proposes a hybrid definition requiring both a fact-based criterion and a value-based criterion.

Results

Wakefield argues that the notion of function and dysfunction are central to the fact component of disorder. Dysfunction implies that there is a failure of some mechanism in the organism to perform its function. This failure is not failure to function in a socially preferred manner, but rather failure to function in the manner it is naturally designed to. Functions can have tremendous explanatory value. Wakefield argues that "natural mechanisms, like artifacts, can be partially explained by referring to their effects, and natural functions, like artifact functions, are those effects that enter into such explanations."(30)

Wakefield goes on to argue that functional explanations have utility even when the actual nature of the mechanism that is dysfunctional is poorly understood. Wakefield then connects his notion of natural function with evolutionary perspective. Evolutionary theory provides an explanation of how a mechanism's effects can explain the mechanism's presence, since those mechanisms whose effects contributed to the reproductive success of the organisms of a species

increased in frequency in the population ("natural selection"). For Wakefield, "dysfunction" is the breakdown of a mechanism that was naturally selected in the process of evolution. Dysfunction, in this respect, is different from an evolutionary maladaptation, since in the case of a maladaptation the naturally selected mechanism remains intact but is no longer well-suited for the organism's current environment.

At the same time, the value criterion of the definition prevents it from collapsing into an evolutionary account. "The mental health theoretician is interested in the functions that people care about and need within the current social environment, not those that are interesting merely on evolutionary theoretical grounds."(30)

DSM takes the approach that what makes a disorder 'mental' is the behavioral nature of the symptoms rather than the kind of dysfunction. But Wakefield argued that for a disorder to be mental, the presence of dysfunction must involve mental mechanisms (30).

On the surface there is a great similarity between the DSM definition of dysfunction (at the time of Wakefield's proposal, it was DSM-III-R) and Wakefield's definition of harmful dysfunction. However, while the DSM-III-R identified dysfunction and harm as two necessary conditions for mental disorder, it did not explicitly describe or define dysfunction, thus providing little meaningful guidance. Utilizing the writings of Spitzer and Endicott, Wakefield shows that the DSM-III operationalizes the concept of harmful dysfunction as "unexpectable distress or disability", which fails to capture the notion of dysfunction as Wakefield envisions it (30).

Conclusion and Critique

Wakefield defines disorder as a harmful failure of a natural function, with 'natural function' referring to functioning as designed in evolution. Wakefield's account has been popular in psychiatry, and in many ways the interpretation of the DSM definition has shifted over time to be more aligned with Wakefield's definition. Robert Spitzer called it "a considerable advance over the DSM definition of mental disorder" (22) and suggested that it should formally be adopted by DSM-5. Allen Frances, chairman taskforce DSM-IV, has praised it: Wakefield "has come up with a definition that works extremely well on paper. His harmful dysfunction and evolutionary perspective provide the best possible abstract definition of mental disorder." (31)

Wakefield's account runs into problems in application to psychiatry for two primary reasons. Firstly, too little is known about the cerebral mechanisms underlying basic psychological functions, and their evolution, to determine with any degree of certainty if a dysfunction of evolutionary design is present. Therefore, the presence of dysfunction in most cases is highly inferential. Secondly, there are many ways for things to 'go wrong' in the psychological realm. While one possibility is failure of a mechanism to perform a function as designed in evolution, there are a number of other possibilities that do not count as dysfunction as Wakefield sees it. The practical implication is that Wakefield's account turns into (in Derek Bolton's words): "a hypothesis that would typically be, for most psychiatric conditions,

uncertain, speculative, provisional, for some quite likely false – and in probably all cases controversial." (32) (p xxv)

Despite these limitations, Wakefield's conceptual analysis of mental disorder and proposed definition have played a tremendous role in redefining the debate, and even philosophical commentators who disagree with his account find it to be the leading objectivist account of mental disorder: "Wakefield's analysis has much to be said for it, and it may well be the best or the only way of providing an objective, scientific basis for the notion of disorder." (32) (p xxiv)

1.6 The Endophenotype Concept in Psychiatry

Citation

Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry. 2003 Apr;160(4):636-45.

Background

Psychiatric disorders have complex genetic underpinnings, and syndromal diagnosis – exemplified by DSM classification – has proven to be non-optimal for genetic research. In the context of genetic theories of schizophrenia in the 1970s, Irving Gottesman and James Shields described "endophenotypes" as internal phenotypes discoverable by a biochemical test or microscopic examination (33); they adapted the term from Bernard John and Kenneth R. Lewis, who had used it to explain concepts in evolution and insect biology. Endophenotypes are measurable entities at an intermediate level, connecting a disease syndrome with the underlying genotype. An endophenotype may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological. Even though the endophenotype concept had been introduced in the 1970s, it did not have much widespread impact in psychiatry until publication of the 2003 review paper, which re-introduced this notion to psychiatry, generating excitement and a large body of research (34). Gregory Miller and Brigitte Rockstroh have called 2003-2013 "the decade of the endophenotype" (10).

Since behavioral syndromes are complex entities with complex genetic underpinnings, endophenotypes are expected to represent relatively less complex phenomena, and the number of genes required to produce variations in endophenotypic traits are expected to be fewer than those involved in producing psychiatric syndromes. Thus, many hoped that we would have better success in linking endophenotypes with genes, and linking endophenotypes with syndromes, rather than linking genes with syndromes directly. In medicine, endophenotype-based methods have been successful in identifying genes related to long QT syndrome, idiopathic hemochromatosis, juvenile myoclonic epilepsy, and familial adenomatous polyposis coli (34).

Methods

Gottesman and Todd Gould reviewed the literature and reintroduced the concept of endophenotypes in the context of intense research into psychiatric biomarkers.

Results

"Endophenotype" is similar to the concept of "biomarker", but a biomarker differs primarily from an endophenotype in that it has no genetic underpinnings. Gottesman and Gould suggested the following criteria for identifying endophenotypes:

1. The endophenotype is associated with illness in the population.
2. The endophenotype is heritable.
3. The endophenotype is primarily state-independent (manifests in an individual whether or not illness is active).
4. Within families, endophenotype and illness co-segregate.
5. The endophenotype found in affected family members is found in nonaffected family members at a higher rate than in the general population.

The article subsequently discusses sensory motor gazing, eye-tracking dysfunction, and working memory as potential candidates for endophenotypes in schizophrenia as salient examples.

Conclusion and Critique

The endophenotype concept was innovative and revitalized research efforts at a time when traditional avenues of research were struggling to tackle the complexity of genetic contributions. Years of research in endophenotypes has led to multiple successes but also humility, as the etiology and pathogenesis of most psychiatric disorders have remained elusive. Many potential endophenotypes have been identified (for instance, executive function and sensory gating in schizophrenia), but there has not been much success yet in finding the genes involved or relevant gene-environment interactions (10). The assumption that endophenotypes in psychiatry would have less complex genetic underpinnings than syndromes has not yet been demonstrated.

Over time, the endophenotype concept led to the realization that existing syndromic, categorical disorders may hinder research; the NIMH thought along similar lines as it developed its RDoC framework. Moreover, most researchers would now agree that is naive to assume that endophenotypes would align along conventional diagnostic lines. Endophenotype research supports a transdiagnostic perspective on mental disorder, and it can be reasonably argued that the RDoC initiative represents a natural extension and elaboration of the endophenotype tradition (10).

1.7 Research Domain Criteria and the Future of Psychiatric Classification

Main Citations

Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010 Jul;167(7):748-51.

Sanislow CA, Pine DS, Quinn KJ, Kozak MJ, Garvey MA, Heinssen RK, Wang PS, Cuthbert BN. Developing constructs for psychopathology research: research domain criteria. J Abnorm Psychol. 2010 Nov;119(4):631-9.

Background

A large body of research has shown that consensus-based diagnostic categories that utilize clinical descriptions of psychiatric syndromes do not align with findings from clinical neuroscience and genetics research. Research findings do not validate the boundaries of DSM constructs in a way we would expect if these constructs represented distinct disease processes. In addition, clinical syndromes do not have high predictive validity with regards to treatment response. All this suggests that the DSM categories are unlikely to capture fundamental mechanisms of dysfunction and etiology.

In this context, the National Institute of Mental Health (NIMH) launched the Research Domain Criteria (RDoC) project to generate a framework for neuroscientific research on the pathophysiology of mental disorders. It is hoped that the RDoC project will create a future classification that better reflects underlying neurobiological mechanisms. The two selected citations are representative articles that introduced this project to the psychiatric community (35, 36).

Methods

The RDoC framework was adapted from a method that had been successfully deployed for studying cognition in schizophrenia, the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) project. The RDoC approach rests on three fundamental assumptions:

1) Mental disorders are brain disorders; i.e. they are complex, multi-level disorders of brain circuitry.
2) Dysfunction in neural circuits can be identified with clinical neuroscience tools, such as electrophysiology, functional neuroimaging, and new methods for quantifying connections *in vivo*.
3) Genetics and clinical neuroscience will yield biosignatures or biomarkers that can refine clinical diagnosis and management.

Results

RDoC can be conceived of as a matrix in which the columns of the matrix represent different levels of analysis, starting with genetic, molecular, and cellular levels, proceeding to the circuit-level, and on to the level of the individual, family environment, and social context. Though the matrix accommodates all levels of biological, psychological, and social analysis in

its framework, the primary focus of RDoC is on neural circuitry. Levels of analysis progress in one of two directions - upwards from measures of circuitry function to variation in clinical function, or downwards to the genetic and molecular/cellular factors. This framework acknowledges that causal influences are multidirectional across levels (e.g., across genes, molecules, cellular systems, neural circuits, and behavior) and is consistent with the idea of "explanatory pluralism" with modest hopes of "patchy reductionism" (28).

The rows of the matrix represent various constructs grouped hierarchically into broad domains of function (e.g., negative emotionality, cognition, etc.). There are five candidate domains in the current conceptualization; the candidate domains were decided by collaborative effort of leading scientists involved in the development of RDoC, and more domains may potentially be added in the future (35, 36):

- Negative affect (negative valence systems): includes constructs that are primarily responsible for responses to aversive situations or context, such as fear, distress, and aggression.
- Positive affect (positive valence systems): includes constructs that aggregate for positive emotionality include reward seeking and learning, and habit formation.
- Cognition: includes constructs dealing with attention, perception, working memory/executive function, long-term memory, and cognitive control
- Systems for social processes: includes constructs that mediate responses in interpersonal settings, such as affiliation and attachment and social communication.
- Arousal/regulatory systems: includes constructs that are responsible for generating activation of neural systems as appropriate for various contexts and providing appropriate homeostatic regulation of such systems as energy balance and sleep.

As an example, Table 2 shows the RDoC matrix for positive valence systems

Construct/Subconstruct		Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Report	Paradigms
Approach Motivation	Reward Valuation								
	Effort Valuation / Willingness to Work								
	Expectancy / Reward Prediction Error								

Construct/Subconstruct		Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Report	Paradigms
	Action Selection / Preference-Based Decision Making								
Initial Responsiveness to Reward Attainment									
Sustained/Longer-Term Responsiveness to Reward Attainment									
Reward Learning									
Habit									

Table 2. RDoC Matrix for Positive Valence Systems (37)

RDoC is by design transdiagnostic; that is, it emphasizes cross-cutting mechanisms for constructs like fear or working memory that can be applied across an array of related diagnoses and deemphasizes conventionally defined mental disorder categories. RDoC research studies are intended to be conducted in clinical samples, but these samples may include one or more DSM disorders (or they may span across clinical syndromes and sub-clinical phenomena) based on a hypothesized shared mechanism of interest, such as fear response across anxiety disorders.

Conclusion and Critique

Critics have argued that the RDoC's emphasis on brain circuitry as the preferred level of explanation will not be applicable to many psychiatric disorders, that the neuroscience models it relies on are insufficiently developed at present, that it leans towards biological reductionism, and that it gives limited consideration to psychosocial factors in psychopathology and treatment (38). These are not fatal criticisms, however, as the RDoC can be expanded to incorporate research insights from the domains of psychology, phenomenology, and social sciences.

NIMH hopes that research conducted within the RDoC framework will lead to new molecular and neurobiological parameters that will predict prognosis and treatment response more successfully than conventional syndromes. Thus, the utility of the RDoC becomes an empirical matter. If research conducted under the RDoC framework leads to the identification of a genetic polymorphism that identifies responders or non-responders to an intervention, or if a copy number variant identifies a subtype with high remission rates, or if a neuroimaging marker in mood disorders predicts lithium response, such findings will have high impact on future psychiatric classification and practice (35, 36).

1.8 Conclusion

While psychiatry has made great advances in the diagnosis and conceptualization of mental illness, significant problems and unanswered questions remain and will continue to preoccupy the field in the future. Kraepelin's hope that a classification based on course of illness would ultimately lead to a classification based on brain pathology has not yet been realized. Operationalized criteria have improved the reliability of diagnosis (though there is still room for improvement, as demonstrated by the DSM-5 field trials (39)), but not yet the validity of diagnosis. Robins and Guze provided a basis for examining the construct validity of a syndromic diagnosis, but validity based on etiological considerations remains elusive. The biopsychosocial model provided a unified framework for a divided psychiatry, but it has declined into a lazy eclecticism in practice, necessitating its evolution into a more sophisticated explanatory pluralism. The RDoC framework represents a potential paradigm shift in psychiatric nosology, with hopes of creating a classification fundamentally based on an understanding of disease mechanisms rather than descriptive phenomenology. Our understanding of the complexity of brain and psychiatric conditions will increase exponentially in the coming decades, and it will be a surprise to none if future conceptualizations of psychiatric conditions are as incommensurable with contemporary views, as the notion of 'mental disorder' is with 'madness'.

1.9 References

1. Compton WM, Guze SB. The neo-Kraepelinian revolution in psychiatric diagnosis. Eur Arch Psychiatry Clin Neurosci. 1995;245:196-201.
2. Shorter E. The history of nosology and the rise of the Diagnostic and Statistical Manual of Mental Disorders. Dialogues Clin Neurosci. 2015;17:59-67.
3. Adityanjee, Aderibigbe YA, Theodoridis D, Vieweg VR. Dementia praecox to schizophrenia: the first 100 years. Psychiatry Clin Neurosci. 1999;53:437-448.
4. Zivanovic O, Nedic A. Kraepelin's concept of manic-depressive insanity: one hundred years later. J Affect Disord. 2012;137:15-24.
5. Engstrom EJ, Kendler KS. Emil Kraepelin: Icon and Reality. Am J Psychiatry. 2015;172:1190-1196.
6. Kraepelin E: Dementia Praecox and Paraphrenia (trans. RM Barclay). Edinburgh, E & S Livingstone; 1919.
7. Kraepelin E: Manic-Depressive Insanity and Paranoia (trans. RM Barclay). Edinburgh, E & S Livingstone; 1921.
8. Kendler KS. Kraepelin and the differential diagnosis of dementia praecox and manic-depressive insanity. Compr Psychiatry. 1986;27:549-558.
9. Ghaemi SN. Bipolar spectrum: a review of the concept and a vision for the future. Psychiatry Investig. 2013;10:218-224.
10. Miller GA, Rockstroh B. Endophenotypes in psychopathology research: where do we stand? Annu Rev Clin Psychol. 2013;9:177-213.
11. Ash P. The reliability of psychiatric diagnoses. J Abnorm Psychol. 1949;44:272-276.
12. Gurland BJ, Fleiss JL, Cooper JE, Sharpe L, Kendell RE, Roberts P. Cross-national study of diagnosis of mental disorders: hospital diagnoses and hospital patients in New York and London. Compr Psychiatry. 1970;11:18-25.

13. Sandifer MG, Hordern A, Timbury GC, Green LM. Psychiatric diagnosis: a comparative study in North Carolina, London and Glasgow. Br J Psychiatry. 1968;114:1-9.
14. Katz MM, Cole JO, Lowery HA. Studies of the diagnostic process: The influence of symptom perception, past experience, and ethnic background on diagnostic decisions. American Journal of Psychiatry. 1969;125:937-947.
15. The diagnosis and psychopathology of schizophrenia in New York and London. Schizophr Bull. 1974:80-102.
16. Kendell RE, Cooper JE, Gourlay AJ, Copeland JR, Sharpe L, Gurland BJ. Diagnostic criteria of American and British psychiatrists. Arch Gen Psychiatry. 1971;25:123-130.
17. Rosenhan DL. On being sane in insane places. Science. 1973;179:250-258.
18. Kendler KS, Munoz RA, Murphy G. The development of the Feighner criteria: a historical perspective. Am J Psychiatry. 2010;167:134-142.
19. Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. Am J Psychiatry. 1970;126:983-987.
20. Feighner JP, Robins E, Guze SB, Woodruff RA, Jr., Winokur G, Munoz R. Diagnostic criteria for use in psychiatric research. Arch Gen Psychiatry. 1972;26:57-63.
21. Spitzer RL, Endicott J, Robins E. Research diagnostic criteria: rationale and reliability. Arch Gen Psychiatry. 1978;35:773-782.
22. Spitzer RL. Harmful dysfunction and the DSM definition of mental disorder. J Abnorm Psychol. 1999;108:430-432.
23. Engel GL. The need for a new medical model: a challenge for biomedicine. Science. 1977;196:129-136.
24. Engel GL. The clinical application of the biopsychosocial model. Am J Psychiatry. 1980;137:535-544.
25. Borrell-Carrio F, Suchman AL, Epstein RM. The biopsychosocial model 25 years later: principles, practice, and scientific inquiry. Ann Fam Med. 2004;2:576-582.
26. Ghaemi SN. The rise and fall of the biopsychosocial model. Br J Psychiatry. 2009;195:3-4.
27. R. MP, R. SP: The Perspectives of Psychiatry. Baltimore, Johns Hopkins University Press; 1986.
28. Kendler KS. Toward a philosophical structure for psychiatry. Am J Psychiatry. 2005;162:433-440.
29. Szasz TS. The myth of mental illness. American psychologist. 1960;15:113.
30. Wakefield JC. The concept of mental disorder. On the boundary between biological facts and social values. Am Psychol. 1992;47:373-388.
31. Frances A: DSM in philosophyland: Curiouser and curiouser. in Making the DSM-5, Springer; 2013. pp. 95-103.
32. Bolton D: What is Mental Disorder?: An Essay in Philosophy, Science, and Values. Oxford, United Kingdom, Oxford University Press; 2008.
33. Gottesman, II, Shields J. Genetic theorizing and schizophrenia. Br J Psychiatry. 1973;122:15-30.
34. Gottesman, II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry. 2003;160:636-645.
35. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010;167:748-751.
36. Sanislow CA, Pine DS, Quinn KJ, Kozak MJ, Garvey MA, Heinssen RK, Wang PS, Cuthbert BN. Developing constructs for psychopathology research: research domain criteria. J Abnorm Psychol. 2010;119:631-639.
37. National Institute of Mental Health. RDoC Matrix. https://www.nimh.nih.gov/research-priorities/rdoc/constructs/rdoc-matrix.shtml (Accessed April 6, 2018).
38. Paris J, Kirmayer LJ. The National Institute of Mental Health Research Domain Criteria: A Bridge Too Far. J Nerv Ment Dis. 2016;204:26-32.

39. Regier DA, Narrow WE, Clarke DE, Kraemer HC, Kuramoto SJ, Kuhl EA, Kupfer DJ. DSM-5 field trials in the United States and Canada, Part II: test-retest reliability of selected categorical diagnoses. Am J Psychiatry. 2013;170:59-70.