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Classification of Depression: Research and Diagnostic Criteria: DSM-IV and ICD-10

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Abstract

This chapter shall address the classification of depressive disorders and its evolution over the past 50 years. We shall present a brief historical overview of depressive disorders and describe the development of the current nomenclature as incorporated in the *Diagnostic and Statistical Manual of Mental Diseases Fourth edition* (DSM-IV) [1] and the *International Classification of Diseases and Related Health Problems 10th edition* (ICD-10) [2]. We will examine current controversies in the diagnosis of depression, and conclude with comments about the potential impact of new neurobiological and neurogenetic developments on the diagnosis of depression in the future.

1.1
Historical Framework

The history of depressive disorders is described in detail by Jackson [3]. The experience of depression has plagued humans since the earliest documentation of human experience. Ancient Greek descriptions of depression referred to a syndrome of melancholia, which translated from the Greek means black bile. In humoral theory, black bile was considered an etiologic factor in melancholia. This Greek tradition referred to melancholic temperament which is comparable to our understanding of early onset dysthymic conditions or depressive personality. During the late 19th and early 20th centuries, phenomenologists increasingly used the term depression or mental depression to refer to the clinical syndrome of melancholia. Emil Kraepelin [4] distinguished mood which was dejected, gloomy, and hopeless in the depressive phase in manic-depressive insanity from the mood which was withdrawn and irritable in paranoia. In addition, Kraepelin distinguished depression which represented one pole of manic-depressive insanity from melancholia, which involves depression associated with fear, agitation, self-accusation and hypochondriacal symptoms.

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Our current classification systems stem from these important observations. The distinction between manic-depressive (bipolar) conditions and non-bipolar conditions remains a critically important objective. The treatments available for these distinct types of disorders are quite different. We continue to rely on best clinical observation, careful diagnostic interviewing and assessment, family history, and clinical course to make these distinctions.

The evolution of formal classification systems is a 20th century phenomenon. The stated goals of any classification system are to ensure improved communication among clinicians, to enhance understanding of the disorders in question, and to promote more effective treatment. Depression researchers have struggled because of the heterogeneity of the depressive syndrome. Early neurobiological investigation of the biological markers, such as cortisol response or cerebrospinal fluid neurotransmitter metabolites thought to be important in the differentiation of depression, yielded few consistent findings. This likely represented the problem of diagnostic non-specificity in the individuals being investigated. The current classification systems hopefully promote better separation between major depressive disorders and bipolar disorder. More accurate separation between psychotic disorders which are schizoaffective versus major depressive disorders with psychotic features is warranted. In addition, it is increasingly relevant to distinguish comorbidity associated with posttraumatic stress disorder from primary depressive disorders, in which trauma may not be a prominent feature.

More than 50 years ago, the evolution of the US diagnostic approach was first typified by the development of the *Diagnostic and Statistical Manual of Mental Disorders, First Edition* (DSM-I) [5]. DSM-I, published in 1952, was prepared by the Committee on Nomenclature and Statistics of the American Psychiatric Association. This revision of psychiatric nomenclature attempted to provide a contemporary classification system consistent with the concepts of modern psychiatry and neurology of that time. It was limited to the classification of disturbances of mental functioning. The diagnostic classification employed the term "disorder" to designate a group of related psychiatric syndromes. Each group was further divided into more specific psychiatric conditions termed "reactions". In this system, the mental disorders were divided into two major groups: (1) those in which a disturbance in mental functioning resulted from or was precipitated by a primary impairment of the function of the brain, generally due to diffuse impairment of brain tissue and (2) those which were the result of a more general difficulty in adaptation of the individual and in which any associated brain function disturbance was secondary to the psychiatric disorder.

For example, psychotic disorders were considered "disorders of psychogenic origin or without clearly defined physical cause or structural change in the brain". Affective reactions such as manic-depressive reactions and psychotic depressive reaction were diagnosed within the psychotic disorders section. Depressive reaction was included within the psychoneurotic disorders in DSM-I.

The *Manual of the International Statistical Classification of Diseases Injuries and Causes of Death* was adopted in 1948 by the World Health Organization [6]. Consistent with the development of DSM-I, international efforts were undertaken

to add an official international classification of mental disorders. In 1948, the World Health Organization (WHO) took responsibility for the sixth revision of the *International List of Causes of Death*, added a mental disorders section, and renamed it the *International Classification of Diseases, Injuries and Causes of Death* (ICD-6) [7]. The section for the classification of mental disorders contained 10 categories of psychosis, nine categories of psychoneurosis, and seven categories of disorders of character, behavior and intelligence.

The mental disorders section of ICD-7 [8] appeared in 1955 and was identical to the section in ICD-6. Because of a lack of international acceptance of DSM-I and ICD-7, the WHO subsequently completed a further evolution of concepts and terms which were included in ICD-8 [9] in 1965. American psychiatrists collaborated in preparation for ICD-8, which was approved by the WHO in 1966 and went into effect in 1968. The effort to revise psychiatric nomenclature and classifications included an effort to upgrade the classification systems in use in the United States which resulted in DSM-II [10].

The nomenclature in DSM-II largely eliminated the concept of reactive conditions, encouraged clinicians to make multiple diagnoses, and incorporated concepts of comorbidity and causation when one disorder was considered to be secondary to another disorder. The DSM-II was published in 1968 and was the result of close collaboration with the international community, such that this system was very similar to the mental disorder section of ICD-8.

Major affective disorders were now considered affective psychoses including involutional melancholia, and manic depressive illness, depressed type. In addition, depressive neurosis replaced neurotic depressive reaction as a general term for non-bipolar depression.

In the early 1970s, several developments were underway that ultimately significantly impacted future diagnostic schemes. International studies comparing classification practices suggested lack of reliability in earlier diagnostic approaches. The development of explicit diagnostic criteria was led by researchers at Washington University School of Medicine including Eli Robins and Samuel Guze, and they developed the first set of diagnostic criteria for research named the Feighner Criteria [11]. In order to meet the needs of a collaborative project on the psychobiology of depression, Spitzer and colleagues modified the Feighner Criteria and added criteria for several additional disorders, resulting in a classification system called the Research Diagnostic Criteria (RDC) [12]. A structured interview called the Schedule for Affective Disorders and Schizophrenia (SADS) [13] was developed to assist researchers in eliciting symptoms necessary for achieving RDC diagnoses. The major revision in American nomenclature was represented in the adoption of DSM-III [14] in 1980. DSM-III was characterized by a dramatic shift in orientation that was descriptive in nature without regard to etiology, and somewhat influenced by the early 20th century concepts of Emil Kraepelin. In this system, explicit diagnostic criteria were used to improve the reliability of classification, more explicit categories for scientific investigation were established, and there was the development of a multi-axial system of evaluation. At the time of the publication of DSM-III in 1980, the international classification did not include a multi-axial system and

did not use explicit criteria for diagnosis. DSM-III represented a dramatic shift away from the principles and diagnostic approaches used in the ICD-9. ICD-9 [15] maintained the approach for depressive disorders outlined in DSM-II and ICD-8.

The predominant change in terminology for depressive disorders incorporated in DSM-III involved the adoption of a primary distinction between major depressive disorders and bipolar disorders. The specific affective disorders included bipolar disorder and major depression distinguished by presence or absence of an episode of mania. Other specific affective conditions such as dysthymic disorder and cyclothymic disorder were considered conditions within the broad category of mood disorders. DSM-III eliminated the diagnoses of depressive reaction and neurotic depression, which characterized the non-psychotic and non-bipolar conditions within DSM-I and DSM-II. Specific descriptive diagnostic criteria were incorporated into the definition of a major depressive episode. Other conditions which did not precisely meet formal criteria for major depressive disorder, single or recurrent episode, bipolar disorder depressed, or dysthymic disorder were considered residual categories such as bipolar type II and atypical depression. DSM-III retained a concept of adjustment disorder with depressed mood.

Other aspects of the changes in DSM-III incorporated the development of a multi-axial system for evaluation that encouraged clinicians to focus attention during the evaluation process on multiple domains of information. Personality disorders were assigned an independent axis in the diagnostic system, which encouraged clinicians to make a diagnosis of major mood disorder on Axis I as well as a personality disorder diagnosis on Axis II. Relevant general medical conditions, important in the evaluation, were diagnosed on Axis III. Assessment of severity and relevant psychosocial or environmental stressors were diagnosed on Axis IV. Global assessment of functioning was coded on Axis V. This multi-axial system of classification represented a marked differentiation from the system in use in ICD-9.

The atheoretical approach to diagnosing mood disorders as well as other conditions in DSM-III was generally accepted among mental health professionals from various disciplines and backgrounds. Researchers with a biological interest as well as researchers with a cognitive–behavioral interest, for example, might approach the investigation of etiology or treatment of mood disorders from different perspectives, but could reliably agree on the descriptive features of diagnosis within an individual. In this regard, the diagnostic criteria in DSM-III were considered useful for purposes of research.

The process of revising DSM-III was supported by the American Psychiatric Association beginning in 1983 and resulted in the publication of DSM-III-R [16] in 1987. Although the revision was intended originally to provide "fine tuning", more substantive changes in diagnostic classification were made reflecting new diagnostic evidence. This relatively short period between DSM-III and DSM-III-R ultimately caused some difficulty for researchers as certain criterion sets were changed.

As indicated before, the international community of psychiatrists had expressed dissatisfaction with the classification of mental disorders in ICD-6 and ICD-7, which meant they were little used. The World Health Organization adopted changes to the mental disorders section which were incorporated into ICD-8. Coinciding with

the changes represented in DSM-III, a classification of mental disorders appeared in ICD-9 which incorporated a glossary as an integral part of the mental disorders section. This glossary offered descriptions of abnormal mental experience or behavior that would serve as a common frame of reference for clinicians. This clinical glossary was distinctively different from the organization of DSM-III which incorporated specific operationalized criteria for diagnosis. The World Health Organization subsequently developed the ICD-9-CM [17], the clinical modification, to describe further the clinical picture of the patient such that the coding would become more precise than that needed only for statistical groupings. The ICD-9-CM went into effect in 1979 prior to the publication of DSM-III. It remains a major tool for collection and dissemination of mortality and morbidity data throughout the world. The current coding used for reimbursement includes the ICD-9-CM codes. However, the definitions for disorders used in DSM-III are not comparable to the specific definitions in ICD-9-CM.

1.2 Current Diagnostic Framework

The process of development for DSM-IV published by the APA in 1994, was guided by specific reviews based upon new empirical evidence for diagnosis. In the classification of mood disorders, the major change in DSM-IV from DSM-III and DSM-III-R includes a listing of nine criterion symptoms of which dysphoric mood or depressed mood or loss of interest or pleasure must be present nearly every day most of the day during a 2-week period. Four additional symptoms associated with a primary depressed mood or loss of interest must be met. Previously, in DSM-III, the criteria of depressed mood or loss of interest were listed as criterion A and four of eight additional symptoms were required for the diagnosis of major depressive episode.

More substantial changes were made in the diagnostic criteria for Dysthymic Disorder. In DSM-III, the diagnosis of depressive mood required 2 years duration and three of 13 criteria in the absence of psychotic symptoms or another pre-existing mental disorder. In DSM-IV, depressed mood most of the day for at least 2 years was required in the presence of two of six criterion symptoms. The exclusion criteria again included a chronic psychotic disorder but other common psychiatric disorders did not pose specific exclusion criteria in diagnosis. In DSM-IV, clinically significant distress or impairment in social, occupational or other important areas in functioning was required. In general, DSM-IV permitted more co-occurring diagnoses to be listed on Axis I without specific exclusion factors. An additional difference in DSM-IV represents the diagnosis of secondary mood disorders, characterized as Mood Disorder Due to a General Medical Condition or Substance- Induced Mood Disorder, in which the disturbance in mood is judged to be a direct effect of a general medical condition or due to substance intoxication, withdrawal or other medication use. The clinician then specifically notes the name of the general medical condition on Axis I or the specific substance involved in intoxication or withdrawal.

The *International Classification of Diseases (ICD), Ninth Revision* maintained the concepts of affective psychoses, in which there may be a severe disturbance of mood accompanied by perplexity, delusions or disorder of perception and behavior consistent with the prevailing mood which included manic-depressive psychosis, depressed type as well as psychotic depressive reaction. The ICD-9 maintained the concept of neurotic depression and depressive personality disorder.

The ICD-10 *Classification of Mental and Behavioral Disorders* largely abandoned the traditional division between neurosis and psychosis that was evident in ICD-9. However, the term "neurotic" was retained as representing a group of disorders called "neurotic, stress-related and somatoform disorders". Instead of maintaining the neurotic–psychotic dichotomy, the disorders are arranged according to major themes or likeness. Classification of affective disorder was particularly influenced with this change such that neurotic depression and endogenous depression are not used, but other types of depression are specified in the affective disorders section such as dysthymia and cyclothymia. In ICD-10, the mood disorders include manic episode, bipolar affective disorder, mild depressive episode, moderate depressive episode, severe depressive episode, recurrent depressive episode, cyclothymia, dysthymia, mixed-affective episode, and recurrent brief depressive disorder.

The description of mood disorder in ICD-10 involves a narrative paragraph with less specific criterion for diagnosis. In addition, severity of the episode represents a distinct syndrome as opposed to a modifier of an episode as is found in DSM-IV.

Table 1.1 outlines differences between the current ICD-10 criteria for depressive disorder and the DSM-IV depressive disorder.

The approach to classification of depressive disorders in DSM-IV and ICD-10 requires a fundamental disturbance in mood, usually depressed mood or loss of interest or pleasure. Neither DSM-IV nor ICD-10 attributes a clear etiology to underlying biochemical processes or considers response to treatment or outcome as factors in the classification of depressive disorder. Definitions of depressive disorder in both ICD-10 and DSM-IV have eight symptoms in common including: depressed mood, loss of interest, decrease in energy or increased fatigue, sleep disturbance, appetite disturbance, recurrent thoughts of death, inability to concentrate or indecisiveness, psychomotor agitation or retardation. The criterion sets differ in that ICD-10 has two additional items: reduced self-esteem or self-confidence and ideas of guilt and unworthiness, whereas DSM-IV combines inappropriate or excessive guilt with feelings of worthlessness (which is qualitatively more severe than loss of self-confidence or self-esteem).

The structure of the diagnostic algorithms also differs between the two systems. ICD-10 groups the items into two sets: one containing three items, depressed mood, loss of interest, and decreased energy; and the other set containing the remaining seven items. The ICD-10 diagnostic thresholds are specified in terms of the number of items required from each of the two sets. DSM-IV instead presents the nine items in one set, but indicates that either depressed mood or loss of interest is required for a diagnosis of Major Depressive Episode.

In ICD-10, separate diagnostic thresholds are established to differentiate between mild, moderate, and severe depressive episodes, depending upon the number of

Table 1.1 Major depressive disorder

	DSM IV	*ICD-10 depressive disorder*
Clinical significance	Symptoms cause clinically significant stress or impairment in social, occupational or other important areas of functioning.	Some difficulty in continuing with ordinary work and social activities, but will probably not cease to function completely in mild depressive episode; considerable difficulty in continuing with social, work or domestic activities in moderate depressive episode; considerable distress or agitation, and unlikely to continue with social, work, or domestic activities, except to a very limited extent in severe depressive episode.
Duration of symptoms	Most of day, nearly every day for at least 2 weeks.	A duration of at least 2 weeks is usually required for diagnosis for depressive episodes of all three grades of severity.
Severity	Five or more of following symptoms; at least one symptom is either depressed mood or loss of interest or pleasure: (1) Depressed mood (2) Loss of interest (3) significant weight loss or gain or decrease or increase in appetite (4) Insomnia or hypersomnia (5) Psychomotor agitation or retardation (6) Fatigue or loss of energy (7) Feelings of worthlessness or excessive or inappropriate guilt (8) Diminished ability to think or concentrate, or indecisiveness (9) Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or suicide attempt or a specific plan	Depressed mood, loss of interest and enjoyment, and reduced energy leading to increased fatigability and diminished activity in typical depressive episodes; other common symptoms are: (1) Reduced concentration and attention (2) Reduced self-esteem and self-confidence (3) ideas of guilt and unworthiness (even in mild type of episode) (4) Bleak and pessimistic views of the future (5) Ideas or acts of self-harm or suicide (6) Disturbed sleep (7) Diminished appetite Typical examples of "somatic" symptoms are: loss of interest or pleasure in activities that are normally enjoyable; lack of emotional reactivity to normally pleasurable surroundings and events; waking in the morning 2 h or more before the usual time; depression worse in the morning; objective evidence of definite psychomotor retardation or agitation; marked loss of appetite; weight loss; marked loss of libido. For mild depressive episode, two of most typical symptoms of depression and two of the other symptoms are required. If four or more of the somatic symptoms are present, the episode is diagnosed: With somatic symptoms. For moderate depressive episode, two of three of most typical symptoms of depression and at least three of the other symptoms are required. If four or more of the somatic symptoms are present, the episode is diagnosed: With somatic symptoms. For severe depressive episode, all three of the typical symptoms noted for mild and moderate depressive episodes are present and at least four other symptoms of severe intensity are required.

symptoms, type of symptoms, and severity of symptoms present. The ICD-10 specifies grades of severity to cover a broad range of clinical sites. Individuals with mild depressive episodes are noted to present in primary care and general medical settings, whereas psychiatry settings are thought to address depressive episodes defined as moderate or severe. In contrast, DSM-IV provides a single nine-item criteria set that gives priority to depressed mood and loss of interest requiring that one of the two be present. In DSM-IV, severity does not determine a separate diagnostic depressive episode, but is assigned instead after the criteria for a major depressive episode have been met. This specifier in DSM-IV is based on the number of symptoms present and level of functional impairment.

An additional differentiation between ICD-10 criteria and DSM-IV involves the presence or absence of psychotic symptoms. In ICD-10, the criteria must be met for a severe depressive episode (eight out of 10 symptoms including depressed mood, loss of interest and decreased energy). If psychotic features, including non-bizarre delusions and hallucinations or depressive stupor are present, then a diagnosis of severe depressive episode with psychotic symptoms may be assigned. Depressive episodes with psychotic symptoms that are less symptomatically severe cannot be indicated using the "psychotic symptom" specifier. In DSM-IV, it is noted that psychotic symptoms typically occur in the most severe cases. It is not always the case and therefore, the DSM-IV subtype labeled "severe with psychotic features" does not require that the individual have all eight depressive symptoms, only that criteria for Major Depressive episode is met and that delusions or hallucinations of any kind must be present. In ICD-10, a clinical significance criterion is not included, while DSM-IV requires that symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

The ICD-10 criteria do not allow for bereavement to be taken into account in the diagnosis, while DSM-IV excludes a diagnosis of major depression if the symptoms of the depressive episode are better accounted for by bereavement.

These differences suggest that much overlap in diagnosis would be present. However, the definitions would lead to some cases in which the criteria for one definition of a depressive episode would be met in one system, but not the other.

The criteria defining recurrence of depression is significantly different in the two systems. ICD-10 requires that the individual has at least 2 months without any significant mood symptoms, whereas DSM-IV requires an interval of at least two consecutive months in which criteria for a major depressive episode are not met. Therefore, ICD-10 is much more stringent, requiring a full remission between episodes, while DSM-IV would consider an individual to have had separate episodes of depression even if symptoms of depression are reduced from five to four within the 2-month period.

DSM-IV provides multiple options for listing specifiers of the current clinical status, including severity, psychotic, and remission specifiers. DSM-IV also includes descriptive features such as chronic, and other descriptive specifiers such as: with catatonic features, with melancholic features, with atypical features, and with post-partum onset. The DSM-IV also includes longitudinal course specifiers such as:

with seasonal pattern and with rapid cycling. Several of these specifiers are not included in ICD-10.

In summary, the two systems provide for many similarities in defining an episode, but the structure of how the episode is diagnosed is somewhat different. DSM-IV makes much more extensive use of diagnostic specifiers, while ICD-10 conceptualizes major depressive episodes as ranging from mild to severe with different symptom thresholds. DSM-IV provides for more specific inclusion and exclusion criteria, which are not contained in ICD-10.

1.3 Controversies

Both DSM-IV and ICD-10 include "not otherwise specified" (NOS) categories in which atypical conditions are defined as conditions not meeting syndromal criteria for a major depressive episode. Sub-threshold forms of depression are important for classification purposes because they are prevalent, have clinical significance in terms of morbidity and functional impairment, and are associated with increased medical care costs and higher rates of service utilization [18–20].

Kessler et al. [21] concluded that mild cases in the DSM system should be retained because attention to a spectrum of impairment highlights the fact that mental disorders (like physical disorders) vary in severity. It is recommended that cost effective treatments for mild disorders might ultimately prevent progression from a mild to a more severe disorder. In contrast, Narrow et al. [22] have proposed that DSM criteria be limited to decrease the number of persons who would meet current criteria, in order to decrease the overall demand for clinical treatment. This proposal limits exploration of the impact of the wide range of symptomatic presentations within the mood disorder spectrum. Removal of current mild cases would limit genetic exploration and examination of both biological and psychosocial risk factors within depressive disorders [23].

Pincus et al. [24] also reviewed the importance of sub-threshold disorders. In DSM-IV, Minor Depressive Disorder requires at least two, but fewer than five depressive symptoms during the same 2-week period. Recurrent brief depressive disorder requires a depressive episode with symptomatic criteria, but lasting less than 2 weeks and requires that the episodes occur at least once per month for 12 consecutive months. In ICD-10, depressive episodes are defined by a systematic symptom threshold, and mild depressive episode requires the presence of four of 10 symptoms. The ICD-10 definition for recurrent brief depressive disorder requires that the depressive episodes last less than 2 weeks, recur once each month over the past year, and fulfill the symptomatic criteria for mild, moderate, or severe depressive episode. In DSM-IV, proposed research criteria for mixed anxiety–depressive disorder are offered, while no criteria are specified for mixed anxiety–depression in ICD-10. The diagnosis of sub-threshold forms of depression are conceptually important for neurobiologic and molecular genetic investigation. They offer research opportunities to examine hypotheses in which consistent neurobiological findings

or susceptibility genes would be present in both severe and mild forms of the disease. However, many prior investigations have excluded individuals with sub-threshold forms of the condition under investigation.

Both DSM-IV and ICD-10 encourage the specification of additional diagnoses in addition to major depressive disorder. The two exclusion criteria defined by DSM-IV include the direct physiologic effects of a substance or a general medical condition and as mentioned above, bereavement. The ICD-10 criteria requires that clinicians follow the general rule of recording as many diagnoses as necessary to adequately capture the clinical picture. Precedence is assigned to that diagnosis most relevant to the purpose of the consultation, and recognition of the lifetime diagnosis is encouraged. The complexity of comorbidity is reviewed in detail by Pincus, Tew and First [25]. The evolution in the second half of the 20th century of ICD and DSM mandated that an increasing number of separate and co-occurring clinical psychiatric conditions and co-occurring personality disorders be recorded as part of a diagnostic evaluation. The increasing diagnostic comorbidity has not yet been addressed conceptually by neurobiologic researchers or incorporated consistently in ongoing neurogenetic and neurobiologic investigation.

1.4 Future Directions

While there is increasing attention being paid to the specificity of criteria in both DSM-IV and ICD-10, no specific etiologic factors are recognized by either classification system. A research strategy that delineates consistent neurobiologic findings within a syndromic classification would result in less diagnostic heterogeneity as compared to a non-etiologic system of classification. The discipline of psychiatry has failed to identify a single biological marker or gene useful in making a diagnosis of major depression.

Furthermore, no biological marker or genetic finding has yet predicted response to a specific pharmacologic treatment. A future classification system in which etiology and pathophysiology are fundamental in diagnostic decision-making would bring psychiatry closer to other branches of medicine. Most likely, many years will pass before such a pathophysiology is delineated or specific genetic findings replicated such that more homogenous syndromes can be identified. Nevertheless, in our opinion, the current syndromic approach offers researchers a continuing opportunity to improve classification systems through ongoing neurobiologic investigation.

1.5 Conclusions

The classification system used for diagnosis of depression has evolved over the past 50 years. Initially, DSM-I underscored the "reactive" aspects of depression and

other psychiatric disorders. Subsequently, DSM-II emphasized the importance of psychodynamic formulations including the differentiation between depressive neurosis and depressive psychosis. More recent DSM systems have offered a non-etiologic paradigm which emphasized nosologic criteria for diagnosis as typified in DSM-III, DSM-III-R, DSM-IV, and DSM-IV-TR [26]. Upon review of the differences in the diagnosis of depressive disorder in DSM-IV-TR and ICD-10, some individuals may be classified differently based on severity or recurrence.

An etiologic or pathophysiologic approach to classification would emphasize disease-specific or symptom-related genes. In addition, phenotypes could be identified based on consistent neurobiologic markers, such as neuroimaging or cognitive function. These neurobiologic or other markers of specific behavior may challenge the validity of our prevailing classification systems. Inevitably, new genetic information would link susceptibility markers with environmental risk factors to explain phenotypic expression. The question remains of whether gene-finding studies or other molecular genetic studies will define specific pathologic syndromes. Alternatively, genetic studies or advances in molecular genetics will identify alterations in intracellular pathways, cellular organization, or neuroanatomic pathways, which are far removed from our current understanding of major depression. The challenges in the future are to develop a broader explanatory understanding of the syndrome under investigation, ranging from basic cellular processes to brain pathways, and their links with relevant psychological constructs such as self-esteem, resilience to stress or stress vulnerability, and personality, temperament, and character.

As reflected in the following chapters, our discipline should be open to emerging neurobiologic and genetic findings as applied to depression. As that understanding grows, classification systems will be modified to include more specific etiologic, pathophysiologic, or pharmacologic substrates of depression.

References

1 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association, **1994**.

2 World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organization, **1992**.

3 Jackson, S. W., *Melancholia and Depression*. New Haven: Yale University Press, **1986**.

4 Kraepelin, E., *Manic-Depressive Insanity and Paranoia*. Translated by Barclay, R. M. Edinburgh, UK: E & S Livingstone, **1921**.

5 American Psychiatric Association. *Diagnostic and Statistical Manual: Mental Disorders*. Washington, DC: American Psychiatric Association, **1952**.

6 World Health Organization. *Manual of the International Classification of Diseases, Injuries, and Causes of Death*. Geneva: World Health Organization, **1948**.

7 World Health Organization. *International Classification of Diseases: Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death, 6th revision*. Geneva: World Health Organization, **1948**.

8 World Health Organization. *International Classification of Diseases: Manual of the International Statistical*

Classification of Diseases, Injuries and Causes of Death, 7th revision. Geneva: World Health Organization, **1955**.

9 World Health Organization. *International Classification of Diseases: Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death, 8th revision*. Geneva: World Health Organization, **1965**.

10 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Second Edition*. Washington, DC: American Psychiatric Association, **1968**.

11 Feighner, J. P., Robins, S. B., Guze, R. A., et al., Diagnostic criteria for use in psychiatric research. *Arch. Gen. Psychiatry* **1972**, *26*, 57–63.

12 Spitzer R. L., Endicott, J., Robins, E., *Research Diagnostic Criteria (RDC) for a Selected Group of Functional Disorders* (3rd ed.). New York State Psychiatric Institute, **1978**.

13 Endicott, J., Spitzer, R. L., A diagnostic interview: The schedule for affective disorders and schizophrenia. *Arch. Gen. Psychiatry* **1978**, *35*, 773–782.

14 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*. Washington, DC: American Psychiatric Association, **1980**.

15 World Health Organization. *International Classification of Diseases, 9th Revision*. Geneva, World Health Organization, **1975**.

16 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*. Washington, DC: American Psychiatric Association, **1987**.

17 World Health Organization. *International Classification of Diseases, 9th Revision, Clinical Modification*. Ann Arbor, Michigan: Commission on Professional and Hospital Activities, **1978**.

18 Horwarth, E., Johnson, J., Klerman, G. L., et al., Depressive symptoms as relative and attributable risk factors for first-onset major depression. *Arch. Gen. Psychiatry* **1992**, *49*, 817–823.

19 Wells, K. B., Stewart, A., Hays, R. D., et al., The functioning and well-being of depressed patients: results from the Medical Outcomes Study. *JAMA* **1989**, *262*, 914–919.

20 Johnson, J., Weissman, M. M., Klerman, G. L., Service utilization and social morbidity associated with depressive symptoms in the community. *JAMA* **1992**, *267*, 1478–1483.

21 Kessler, R. C., Merikangas, K. R., Berglund, P., et al., Mild disorders should not be eliminated from the DSM-V. *Arch. Gen. Psychiatry* **2003**, *60*, 1117–1122.

22 Narrow, W. E., Rae, D. S., Robins, L. N., et al., Revised prevalence estimates of mental disorders in the United States: using a clinical significance criterion to reconcile 2 surveys' estimates. *Arch. Gen. Psychiatry* **2002**, *59*, 115–123.

23 Benjamin, J., Ebstein, R. P., Lesch, K. P., Genes for personality traits: implications for psychopathology. *Int. J. Neuropsychopharmacol.* **1998**, *1*, 153–168.

24 Pincus, H. A., McQueen, L. E., Elinson, L., Subthreshold mental disorders. In Phillips, K. A., First, M. B., Pincus, H. A. (Eds.), *Advancing DSM: Dilemmas in Psychiatric Diagnosis*. Washington, DC: American Psychiatric Press, Inc.**2003**, 129–144.

25 Pincus, H. A., Tew, J. D., First, M. B., Psychiatric comorbidity: Is more less? *World Psychiatry* **2004**, *2 (3)*, 153–158.

26 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*. Washington, DC: American Psychiatric Association, **2000**.