CLASSIFICATION OF PSYCHOSIS

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Correction: The subtitle "Unsystematic Schizophrenias" on page 67 should read "Unsystematic and Systematic Schizophrenias".

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Preface

Nosology is one of the main disciplines which provide a solid foundation for modern psychiatry. It deals with the identification (diagnosis) and classification of mental disorders, i.e., with the ordering of disease entities which are derived from a synthesis of pathologic subjective experiences (e.g., hallucinations) and abnormal objective performances (e.g., amnesias)[1].

It was in the **MEDICAL DICTIONARY** of **ROBERT JAMES**, published in 1743, that the term nosology first appeared; and it was in **FRANCOIS BOISSIER DE LA CROIX DE SAUVAGES'** (1768) treatise, **NOSOLOGIA METHODICA**, that it was first used in reference to the taxonomy of "mania," i.e., mental illness.

The importance of nosology for psychiatric practice and research cannot be over-emphasized, because it is nosologic knowledge that provides the necessary diagnostic end-points for the identification of clinically meaningful and biologically homogenous categories of mental illness. Furthermore, because it is nosology that provides the conceptual framework that allows for an understanding of how the different disease categories and classifications are derived,

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[1] The origin of the notion, that psychiatric disorders result from a synthesis of pathologic subjective experiences and abnormal performances, was in the work of Claude Bernard (1865), Charles Sherrington (1906) and Ivan Petrovich Pavlov (1927) . Bernard's idea of "internal synthesis" and Sherrington's recognition of the "integrative action of the nervous system", were instrumental in Pavlov's conceptualization of brain activity in terms of "excitation" and "inhibition", and the results of this activity, in terms of "analysis" and "synthesis" (Ban, 1964).

without an adequate understanding of nosology, training in psychiatry, i.e., the learning of when and what to do, cannot be considered a psychiatric education, i.e., a learning of why to do it.

There are many difficulties in teaching psychiatric nosology within the traditional medical curriculum. Among them, one of the most important is, that with the exception of neuropsychiatric disorders[2], the biologic substrate of mental illness has not been resolved by traditional histologic and/or neurochemical methods. The same applies to modern brain imaging techniques, such as magnetic resonance imaging and positron emission tomography. Because of this, there is no consensus whether the term, disease, should be applied to any other categories of psychiatric disorders.

Consensus, regarding the nature of mental illness, has not increased with the recognition that a considerable proportion of drugs, with a detectable action on the synaptic

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[2] In the DSM-III-R (American Psychiatric Association, 1987), the term, neuropsychiatric disorders, is an all embracing concept, which includes all Axis I diagnoses; whereas in the ICD-9 (World Health Organization, 1977), it is a restricted concept which is used only, in reference to the diagnoses included under psychoses. In this monograph, the term neuropsychiatric disorders, refers to disorders which are associated with and/or are the result of a neuropathologic process, i.e., identifiable neuropathologic changes.

cleft[3], have therapeutic effects (in sui generis psychiatric disorders[4]). One possible reason for this is, that findings in clinical psychopharmacologic studies have fallen short of predicting the treatment responsive population. Another possible reason is the lack of success in linking the results of neuropharmacologic research to empirically derived disease categories of mental illness. It is indeed a fact, that neither the findings of clinical psychopharmacologic studies, nor the results of neuropharmacologic research, have entirely ruled out the possibility, that "there are no disease entities in clinical psychiatry, but only varieties of madness with florid boundaries

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[3] The mammalian brain contains millions of nerve cells (neurons) with many billions of interconnections. The great majority, but not all of these connections, involve a process of chemical transmission at the site of the synapse, in which the arrival of a nerve impulse, through the presynaptic neuron, leads to the release of a minute amount of neurotransmitter substance. In case of chemical transmission, the released chemical transmitter rapidly diffuses across the narrow synaptic cleft and acts upon specialized receptor sites on the surface of the postsynaptic neuron (Iversen and Iversen, 1975, 1981). Recognition that pharmacologic substances with a measurable effect on synaptic processes have an effect on both, behavior and psychopathologic symptoms, opened the path for modern neurobiologic research in psychiatry.

[4] The term, sui generis psychiatric disorders, refers to all the different conditions which are included under functional psychiatric disorders, i.e., the endogenous psychoses, the reactive psychoses and the neuroses. They are conceptualized as pathologies in the processing of experience, which are possibly the result of pathologies in the transmission of impulses at the synaptic cleft.

of their own which merge into each other" (Jaspers, 1962)[8].

The second difficulty in teaching psychiatric nosology is the lack of agreement regarding the nature of the manifestations in which mental illness is expressed, e.g., subjective experiences (phenomenology), objective performances, social behavior. This difficulty is compounded by the finding that social behavior, which can probably be assessed more reliably than subjective experience, is contingent upon a multitude of factors and, is therefore, the least valid in expressing the psychiatric disease process.

Finally, the third, and from a practical point of view the greatest difficulty encountered in teaching psychiatric nosology is, that it is not known which, if any, of the conceptually derived, and/or consensus-based classifications, such as the French INSERM, the American DSM, or the international ICD, could provide a valid nosology of psychiatric disorders.

The main purpose of this series of monographs is to open discussion on all three of these intrinsically linked issues. It is also hoped that by the presentation of the current state of affairs, from three different perspectives, in the three parts of

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[8] The differential therapeutic responsiveness to psychotropic drugs is in variance with the notion that there is only one, single, psychiatric disease.

this series[6], PSYCHIATRIC NOSOLOGY will provide clinicians, teachers and researchers with a useful frame of reference for the diagnosis and classification of mental disease.

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[6] In the three parts of this series Consensus Based Classifications (Part One), Conceptually Derived Classifications (Part Two) and Composite Diagnositic Evaluations (Part Three) will be reviewed and discussed.

Introduction

The term, neurosis was introduced in 1769 by **WILLIAM CULLEN** in his **SYNOPSIS NOSOLOGIAE METHODICAE.**[7] Originally, neurosis was an all embracing concept, corresponding to the belief that "all the diseases with their seat in the nervous system are associated with, and/or result in, mental derangement" (Littre, 1877).

To shift emphasis, in the assumed substrate (etiology) of mental derangement, from the nerves, as postulated by Cullen (1769), to the soul (psyche)--perceived as the "corporalized spirit" (Feuchtersleben, 1845)--the term, "Psychiaterie" was introduced by **JOHANN CHRISTIAN REIL** in 1803, in his book **RHAPSODIEN UBER DIE ANWENDUNG DER PSYCHISCHEN CURMETHODE AUS GEISTESZERRUTTUNGEN.**[8] The term was adopted by **JOHANN CHRISTIAN HEINROTH** (1818), and changed to Psychiatrie (psychiatry) in his **LEHRBUCH DER STORUNGEN DES**

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[7] Cullen believed that "life is a function of nervous energy, muscle a continuation of nerve, disease, mainly nervous disorder, and fever an effect of diminished cerebral power from local (external) lesions". Accordingly, he classified diseases into four categories, i.e., fevers, neuroses, cachexias and local disorders. The broadest, among these categories, was the category of neuroses, which included a wide variety of disorders, including gout (Garrison, 1913, 1960).

[8] Separation of body and mind, i.e., Cartesian dualism, was introduced into psychiatry through Reil's work, approximately 150 years after the publication of RENE DESCARTES' monumental treatise, MEDITATIONES DE PRIMA PHILOSOPHIA IN QUIBIS DEI EXISTENTIA, ET ANIMAE HUMANAE A CORPORE DISTINCTIO, DEMONSTRANTUS (MEDITATIONS ON FIRST PHILOSOPHY, IN WHICH THE EXISTENCE OF GOD AND THE DISTINCTIVENESS BETWEEN MIND AND BODY ARE DEMONSTRATED), in 1642. It was in MEDITATIONS, that Descartes first postulated the absolute duality of body and mind, arguing that the two are irreducibly heterogenous and that one does not interact with the other.

SEELENLEBENS.

In subsequent years, the term, psychiatry, and with the word, the conceptualization of mental disorders as disorders of the mind, profoundly affected the subject matter of the field. This is, to the extent, that, to-date, psychiatric opinion has remained divided as to whether psychiatry deals with Cullen's (1769) disorders of the nerves (i.e., body), or Reil's (1803) disorders of the soul (i.e., mind).[9]

By the 1840's, the term, neurosis, referring to "all the diseases of the body which were assumed to have their seat in the nervous system,"[10] and the term, psychiatry, or psychiatric disorders, referring to all the disorders of the mind which were assumed to be caused by the "corporalized spirit," were used interchangeably. Recognition, however, that not "every defect of the nervous system

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[9] ARTHUR KOESTLER (1967) in his book, THE GHOST IN THE MACHINE, referred to the introduction of Cartesian dualism, as to the "Cartesian catastrophy". It was Cartesian dualism which opened the path for the belief, that psychiatry deals with the disorders of a spiritual mind which is trapped in a physical body.

[10] By the end of the 20th century, the concept of neurosis had lost its original meaning. In the Glossary of Technical Terms of the DSM-III, published in 1980, it was defined as a "mental disorder in which the predominant disturbance is a group of symptoms that is disturbing, unacceptable and ego-dystonic. In patients with neuroses reality testing is grossly intact; and behavior does not actively violate group social norms". In the same glossary a neurotic process was defined as a specific etiologic process in which "unconscious conflicts cause unconscious perception of anticipated danger, leading to the use of defense mechanisms that result in symptoms and/or personality disturbance". The term, neurosis, is not included any longer in the Glossary of Technical Terms of the DSM-III-R, published in 1987. It is interesting that the last definition of the concept (which appeared in the DSM-III) was more in keeping with Reil's conceptual framework, than with Cullen's.

is necessarily accompanied by a mental disorder," although "every mental disorder implies the existence of a disease of the nervous system" (Pichot, 1983), led to the introduction of the concept and term, psychosis, by **ERNST FEUCHTERSLEBEN**. In his **LEHRBUCH DER ARZTLICHEN SEELENKUNDE**, published in 1845, Feuchtersleben declared that "every psychosis is at the same time a neurosis, because, without the nerves as intermediaries, no psychologic change can be exhibited, but not every neurosis (i.e., disorder of the nerves) is a psychosis"--using the term psychosis for the first time in the psychiatric literature.

For some time, the term, psychosis, and the term, psychiatric disorder, were used interchangeably[11]. The new concept opened the road, however, for the separation of the disorders of the nerves, which affect the mind, from the disorders of the nerves, which have no such an effect. In the ultimate analysis, it was the introduction of the concept of psychosis which, by separating neurologic disorders from psychiatric disorders, provided the necessary frame of reference, for the development of the discipline referred to as psychiatry today.

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[11] During the mid-19th century the three terms, psychosis, psychiatric disorder and insanity (or insania, the term used by Celsus in the third book of his De Re Medicina), were used interchangeably.

Monograph One

CLASSIFICATION OF PSYCHOSES

Definition of Psychosis

Introduced in 1845 by Feuchtersleben, in order to separate neuropsychiatric disorders (neuroses) from psychiatric disorders (psychoses), the term, psychosis, has remained vaguely defined with fluid boundaries and changing diagnostic criteria.[12] In the original definition it was an all embracing concept. However, with the publication of **JASPERS'** (1910) classic paper, **EIFERSUCHTSWAHN: ENTWICKLUNG EINER PERSOENLICHKEIT ODER PROZESS**, and the separation of developmental anomalies from the results of disease process, the scope of psychosis was restricted to the "effects of illness".

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[12] In FISH's (1967) CLINICAL PSYCHOPATHOLOGY, psychosis was defined as a "distortion of the whole personality with lack of insight, construction of false environment (out of subjective experiences), gross disorder of basic drives (including self-preservation) and inability to make a reasonable social adjustment." (Hamilton, 1985). In contrast, in the ENCYCLOPEDIA OF PSYCHIATRY FOR GENERAL PRACTITIONERS, edited by LEIGH, PARE and MARKS (1972), "the term, psychosis refers to mental illness which is severe, produces conspicuously disordered behavior, cannot be understood as an extension or exaggeration of ordinary experience and whose subject is without insight". Somewhat similar, in the ICD-9 of the WORLD HEALTH ORGANIZATION (1977), psychoses are defined as "mental disorders in which impairment of mental function has developed to a degree that interferes grossly with insight, ability to meet some ordinary demands of life or to maintain adequate contact with reality." In both, the DSM-III and DSM-III-R of the AMERICAN PSYCHIATRIC ASSOCIATION (1980, 1987), "direct evidence of psychotic behavior is the presence of either delusions or hallucinations without insight into their pathological nature". However, "the term psychotic is (considered to be) sometimes appropriate (also) when a person's behavior is so grossly disorganized that a reasonable inference can be made that reality testing is markedly disturbed". In the ICD-10 of the World Health Organization (1990), the term, "psychosis is retained, but it is left deliberately without any attempt of definition".

For Jaspers' (1913), psychosis was "the result of a disease process which seizes upon the individual as a whole, regardless of whether it is a hereditary disorder beginning at a certain time of life, or a non-hereditary disorder which is called into being by an exogenous lesion." To qualify for psychosis, the pathologic process had to be sufficiently strong to override normal development; and the behavior displayed sufficiently different, that it could not be understood as an extension of the normal and/or an exaggerated response to ordinary experience.

Jaspers' (1913) criteria of psychosis were adoped by **KURT SCHNEIDER** (1950), who in his **KLINISCHE PSYCHOPATHOLOGIE**, separated "anomalies of development", or "abnormal variations of psychic life", from "psychoses", i.e., "effects of illness".

Unitary Psychosis

Development of the Concept

In its original formulation, the concept of psychosis implied that all the different mental syndromes are based on detectable morphologic changes and identifiable diseases of the "nerves". Recognition, however, that this is not the case, led **WILHELM GRIESINGER** (1861) to postulate, that different mental syndromes represent different developmental stages of one and the same

pathologic process.[13] In his classic text, **DIE PATHOLOGIE UND THERAPIE DES PSYCHISCHEN KRANKHEITEN**[14], he adopted the notion, that in the mental syndromes in which neuropathologic changes are absent, they will become detectable at a later stage of disease development.[15]

The origin of Griesinger's(1861) unitary concept of psychosis was in the work of Bayle (1822), who was the first to report that in chronic arachnoiditis, the dementia syndrome displayed in "état de démence", was preceded by other mental syndromes during the

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[13] OTTO M. MARX (1972) in his paper on WILHELM GRIESINGER AND THE HISTORY OF PSYCHIATRY: A REASSESSMENT, summed up Griesinger's concept of unitary psychosis as follows: "Viewing all mental illness as a part of one process, Griesinger proposed that in its initial phase, characterized by the dominance of certain pathological efforts, mental illness was unaccompanied by structural changes in the brain, and hence reversible. Brain structure was affected in the second phase in which mental image formation, or will was affected. Irreversible structural changes, and symptomatology typical of the second phase or of the third phase (characterized by deterioration), implied incurability."

[14] GRIESINGER'S monograph was first published in 1845. However, the concept of unitary psychosis was first presented in the second edition, published in 1861. The monograph was translated from the second edition of the German original into English by C. LOCKHART ROBERTSON and JAMES RUTHERFORD, under the title MENTAL PATHOLOGY AND THERAPEUTICS. The English edition was published in 1867 by The New Sydenham Society in London. The third and last edition of the monograph was published in 1871.

[15] Prior to the publication of the second edition of Griesinger's monograph in 1861, in which the crystallized concept of unitary psychosis first appeared, a similar concept was presented by GUISLAIN in 1833, in his TRAITÉ DES PHRÉNOPATHIES, and by NEUMANN in 1859, in his LEHRBUCH DER PSYCHIATRIE (Crow, 1986).

first and second stages of disease development.[16] Considering that these syndromes corresponded with the second ("délire monomaniaque") and the third ("délire maniaque") syndromes in Esquirol's (1838) classification, and the dementia syndrome corresponded with the fourth syndrome, i.e., with the syndrome associated with structural changes in the brain,[17] Griesinger (1861) felt justified in adopting Bayle's findings, derived from the analysis of a neuropsychiatric condition, as a <u>model</u> of mental disease, i.e., unitary psychosis.

<u>Place in Nosologic Development</u>

There are several divergent views regarding the place and role of unitary psychosis in the conceptual development of diagnosis and classification of psychiatric disorders. In Lehmann's (1971) view, by the mid-19th century a widespread interest in the nosology of mental disease had crystallized and with it "an open controversy

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[16] In his RECHERCHES SUR LES MALADIES MENTALES, originally published as a thesis, BAYLE (1822) put forward the notion that "the symptoms of chronic arachnoiditis (arachnitis) can all be reduced to a general and incomplete paralysis and to the derangment of the intellectual faculties. These two orders of phenomena proceed at an equal and proportional pace and allow the disease to be divided into three periods, i.e., délire monomaniaque, with exaltation in the first, délire maniaque, accompanied by dominant ideas in the second, and état de démence, in the third" (Pichot, 1983).

[17] Esquirol (1838) distinguished among five "general forms of insanity": (1) lypemania or melancholy of the ancient, (2) monomania, (3) mania, (4) dementia and (5) imbecility or idiocy.

had developed between those who wanted a classification according to causes and those who wanted a classification according to symptoms."[18] Simultaneously, there was also a "violent controversy" between psychiatrists who, like Griesinger (1845), saw mental disease as a "disorder caused by physical brain disease",[19] and psychiatrists who, like Heinroth (1818), looked at mental disorders

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[18] According to Lehmann (1971) "The old controversies of the 'symptomatologists' versus the 'etiologists', and of the 'organicists' versus the 'dynamicists' have survived a century and are still very much part of our ongoing discussions in modern psychiatry which has added one other fundamental controversy. Stengel calls it a controversy between the 'separatists' and the 'gradualists'. The separatists conceive of the psychoses as autonomous disease entities which are qualitatively different from the neuroses and character disorders. The gradualists, led by Menninger and Ey, advocate a unitary concept of mental diseases, and see mental pathology distributed on a continuum from the normal to the psychotic, which is, according to this school, only quantitatively different from the neurotic, i.e., sicker."

[19] The first (two) paragraph(s) of GRIESINGER's (1867) MENTAL PATHOLOGY AND THERAPEUTICS read: "The following treatise has for its object the study of mental disease or insanity, its diagnosis and treatment. Insanity itself, an anomalous condition of the faculties of knowledge and of will, is only a symptom; our classifications of the group of mental diseases proceeds upon the symptomatological method, and by such a method alone can any classification be effected. The first step towards a knowledge of the symptoms is their locality--to which organ do the indications of the disease belong? What areas must necessarily and invariably be diseased when there is madness? The answer to these questions is preliminary to all advancement in the study of mental disease.

Physiological and pathological facts show us that this area can only be the brain; we therefore primarily, and in every case of mental disease, recognize a morbid action of that organ."

as "the result of dynamic, psychologic and spiritual struggles".[20] According to Lehmann (1971), it was "reacting to this confusion" that Neumann (1859) declared, that psychiatry would only be able to progress if it decided to "throw overboard the whole business of classification," and adopted the unitary concept of psychosis.

A completely different view regarding the place and role of unitary psychosis on the conceptual development of psychiatric diagnosis and classification was presented by Pichot (1986). In variance with Lehmann (1971), he suggested that the increase of interest in nosology during the last quarter of the 19th century, was triggered by Griesinger's (1867) formulation of the concept of unitary psychosis.

Psychopharmacologic Considerations

The initial clinical studies with chlorpromazine,[21] the first

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[20] HEINROTH's monograph, LEHRBUCH DES STORUNGEN DES SEELENLEBENS, was published in 1818. It represents an "ethico-religious line of mentalism" in which "mental disease is by nature a loss of liberty and the result of sin and misdeeds" (Pichot, 1983).

[21] The basic constituent of chlorpromazine is the phenothiazine nucleus which consists of two benzol rings attached to each other by a sulfur and a nitrogen atom. It was synthesized on December 11, 1950 by Charpentier and his collaborators (1952); released for clinical studies by May 2, 1951, upon completion of the intitial pharmacological investigations by Courvoisier and her team (1953), and had been tried as an autonomic stabilizer (Laborit, Huguenard and Alluaume, 1952) to bring about a condition that Laborit (1952) described as 'artificial hibernation' within the same year (Ban, 1972).

clinically employed neuroleptic[22], were carried out approximately 100 years after the introduction of the concept of unitary psychosis. They were conducted at a time, when the nosologic concept of unitary psychosis had long been replaced by a number of different diagnostic concepts of functional and organic psychoses. Because of this, it could readily be seen, that the therapeutic effects of chlorpromazine, did not distinguish among, and cut across the diagnostic boundaries of different psychoses. Considering that chlorpromazine (and other subsequently developed neuroleptics) were able to control psychopathologic symptoms, which could lead to construction of false environment out of subjective experiences, Lehmann (1961) referred to neuroleptics as antipsychotic drugs. He did not imply, however, that the different antipsychotic (i.e., neuroleptic)-responsive syndromic diagnoses,

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[22] The term neuroleptic, was first used by Delay and Deniker in 1955 to replace the term "neuroplegic", the term used by Laborit in 1952 to characterize the action of chlorpromazine (Caldwell, 1970). In 1967 the World Health Organization adopted the term neuroleptic for drugs, which similar to chlorpromazine, have "therapeutic effects in psychoses and other types of psychiatric disorders and are accompanied in their action by certain neurological effects such as extrapyramidal signs" (Ban, 1969). However, SHEPHERD (1990) in his recent paper THE NEUROLEPTICS AND THE OEDIPUS EFFECT published in the Journal of Psychopharmacology, pointed out "that the widespread use of the term 'neuroleptic' in preference to the many alternatives that were originally suggested -- for example 'ataractics', 'tranquilizers', 'deturmoilizers', 'antipsychotics', 'anti-schizophrenics', etc. -- has no more than what even one of its advocates has admitted to be 'frail' scientific value (Collard, 1974). For this reason the committee responsible for the WHO Lexicon on Psychiatric and Mental Health Terms has recently proposed that 'neuroleptic' be defined as follows: A term applied by Jean Delay and Pierre Deniker to drugs, phenothiazines, reserpine, alkaloids, butyrophenones, whose supposedly specifically antipsychotic action is associated with the induction of a neurological syndrome of the extrapyramidal type. The value of the term is dubious and its use is to be deprecated. The comments received so far from an international panel of experts indicate that the definition commands general assent."

were an integral part of one and the same disease process.[23]

If therapeutic responsiveness to chlorpromazine during the acute phase of treatment alone would suffice as an acceptable validation criterion for a diagnosis, the results of the initial clinical studies with chlorpromazine[24] were in support of unitary psychosis.[25] Considering, however, that this is not the case, and that

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[23] Lehmann (1971), in his presentation at the International Collegium on Psychosis, held in 1969 in Montreal, made his position regarding unitary psychosis clear by the following statement: "One effect the advent of pharmacotherapy has had on clinical psychiatry may be considered detrimental to nosology, i.e., the immediate use of neuroleptic drugs in acute psychotic conditions before an adequate diagnosis has been established...The situation is not unlike that encountered in internal medicine, where the premature application of antibiotics in bacteremia, or of morphine in acute abdominal pathology, might obscure the precise diagnosis. At our hospital, we have a standing rule prohibiting the continued use of neuroleptic drugs in newly admitted patients until a definite diagnosis has been made."

[24] The first clinical study using chlorpromazine with psychiatric patients was conducted by Hamon, Paraire and Velluz (1952) at Val de Grace, the famous military hospital in Paris. It was followed by the initial clinical studies of Delay and Deniker (1952) in France, Staehelin and Kielholz in Switzerland (1953), and Lehmann and Hanrahan (1954) in Canada (Caldwell, 1970; Ban, 1972).

[25] Similar therapeutic effects on psychotic manifestations in different disorders suggest a common biologic anomaly of psychotic manifestations which is affected by the drug, and not of a common biologic basis of the different disorders. Because of this, only by stretching the concept of unitary psychosis into the concept of psychotic spectrum disorders could one consider that the findings of similar therapeutic effects with chlorpromazine in different disorders is supportive of unitary psychosis. In no way could one consider it supportive of the contention that different clinical syndromes are different stages of one and the same pathologic (disease) process.

therapeutic effects with neuroleptics show great variations with continuation of treatment, the similar therapeutic response during the acute phase[26], cannot be interpreted as supportive of a unitary concept of mental illness. On the other hand, it indicates, that chlorpromazine can control certain target symptoms[27], commonly seen in the acute phase of different psychoses, regardless of the diagnosis.

Somatically Determined Psychoses

While the recognition that not all mental syndromes are associated with detectable morphologic changes in the brain, yielded the unitary concept of mental illness, the recognition that not all mental disorders lead to detectable neuropathologic changes, resulted in the dissolution of the nosologic concept of unitary psychosis. In the ultimate analysis, however, it was the

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[26] Therapeutic response to a particular drug during one developmental stage of an illness alone does not suffice as a validation criterion for a nosologic (diagnostic) concept. On the other hand, similar therapeutic response in all the different developmental stages of an illness, qualifies for a validation criterion.

[27] The term, target symptoms was first used by Freyhan (1955) for the specific symptoms which are selectively affected by chlorpromazine. Since the late 1950s the term has been in use in a broader sense for the different symptoms that are selectively affected by psychotropic drugs. Similar to the antipsychotic concept of Lehmann (1961), the essence of Freyhan's target symptom concept is, that the effect of drugs, such as the antipsychotics (neuroleptics) is not on nosologic (i.e., etiologic) entities, but on the manifestations (i.e., the biologic substrate of the final common path) of psychosis.

development of a clinical methodology with the capability to indicate the presence of neuropathologic changes from psychopathologic symptoms with a high level of probability,[28] that led to the formulation (and separation) of the nosologic (etiologic) concepts of organic and functional psychoses.[29]

The importance of the new methodology, and the possible separation of the organic from the functional by the employment of the new methodology, cannot be over-emphasized. It represents the first major breakthrough in the diagnosis and classification of mental illness. The new clinical methodology opened the path for development, that led to the identification of psychoses linked with somatic illness; and to the separation of the somatically

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[28] The clinical methodology, which has the capability to detect neuropathologic changes from psychopathologic symptoms and signs with a high level of probability, is general psychopathology. The discipline, psychopathology is concerned with "every psychic reality which can be rendered intelligible by a concept of constant significance" (Jaspers, 1962); whereas the methodology, general psychopathology, deals with the identification, description and conceptualization of the signs and symptoms of psychiatric disorders.

[29] The choice of the terms, such as organic and functional, is unfortunate, because functional, if contrasted with the organic, implies that functional psychoses are disorders of the mind, and unlike the organic psychoses, they are not biologic (in nature). Because of this, according to Cobb (1952), "considerable confusion attends the application of terms, such as organic and functional." However, Mayer-Gross, Slater and Roth (1954) maintained that "no one so far has been able to suggest satisfactory alternatives to them".

determined psychoses, from the structurally determined psychoses.[30]

Organic Psychosis

The origin of the nosologic concept of organic psychosis, the first clinically identified somatically determined psychosis, was in Bayle's (1822) observations,[31] that chronic (irreversible) neuropathologic changes are linked with "general paralysis" and "derangement of the intellectual faculties".[32]

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[30] In the dichotomy of somatically and structurally determined psychoses, somatically determined implies that the clinical psychopathology is linked with, and secondary to, another somatic illness. In contrast, structurally determined implies, that there is no other somatic illness, and that the structure displayed is the only recognizable manifestation of the disease process.

[31] BAYLE's observations and conceptualizations relevant to the development of the diagnostic concept of organic psychosis were described and presented in his three monographs. The first, RECHERCHES SUR L'ARACHNITIS CHRONIQUE...CONSIDERÉES COMME CAUSE D'ALIENATION MENTALE, was published in 1822; the second, NOUVELLE DOCTRINE DES MALADIES MENTALES, was published in 1825; and the third, TRAITÉ DES MALADIES DU CERVEAU ET DE SES MEMBRANES, was published in 1826. Nouvelle Doctrine, dealt primarily with the delusional syndromes displayed preceding the onset of detectable dementia. Because of its subject matter, NOUVELLE DOCTRINE played an important role in the development of the unitary concept of psychosis. However, probably more important is, that the clinical descriptions in NOUVELLE DOCTRINE are in keeping with the belief that delusional syndromes are disinhibited subcortical patterns, which would have remained silent without the cortical damage produced by the neuropathologic process (Berrios, 1981, 1989; Pichot, 1983).

[32] Since 1822 there have been considerable changes in the accessible technology for the detection of structural changes in the brain. They include advances in in-vitro histopathologic techniques, and advances in in-vivo techniques, such as brain imaging.

In subsequent years, the diagnostic concept of organic psychosis, i.e., mental illness which is characterized by an intrinsic link between the dementia syndrome[33] and neuropathologic changes, received substantial support.[34] It was also recognized that in terms of its etiology the dementia syndrome is nonspecific. Because of this, organic psychosis, a diagnostic concept, does not qualify for a distinctive nosologic entity. It is a syndrome, which indicates that a somatic disease, by causing brain injury, has produced irreversible neuropathologic changes, which are displayed by distintegration of mental (intellectual) faculties.

Exogenous Psychosis

The origin of the nosologic concept of exogenous

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[33] The dementia syndrome consists of personality deterioration and loss of intelligence. Jaspers (1962) defined intelligence as the "totality of all the abilities of an individual", i.e., "the instruments of performance and purpose which are available for an individual for adaptation to life". Somewhat similar, Fish (1967) defined intelligence as the "ability to think and act rationally and logically", that can be "measured by testing the ability of an individual to solve problems, to form concepts by the use of words, numbers, other symbols, patterns and non-verbal material".

[34] Supportive of the diagnostic concept of organic psychosis are the findings that in disorders such as Huntington's chorea, first described in 1872, Pick's disease, first described in 1892, Alzheimer's disease, first described in 1907, and Jakob-Creutzfeldt's disease, first described in 1920 (Creutzfeldt, 1920; Jakob, 1921), the different neuropathologic processes are displayed in a similar disintegration of mental faculties.

psychosis[35], the second clinically identified somatically determined psychosis, was in Bonhoeffer's (1909, 1910)[36] observations, that delirium, epileptiform reactions, stupor, and confusional states[37], are intrinsically linked with physical illness

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[35] In the DSM-II (American Psychiatric Association, 1968), the term, acute brain syndromes, was used in reference to exogenous psychoses.

[36] BONHOEFFER's observations and conceptualizations relevant to the development of the nosologic concept of exogenous psychosis were described and presented in his paper, ZUR FRAGE DER EXOGENEN PSYCHOSEN, published in 1909; and in his monograph, DIE SYMPTOMATISCHEN PSYCHOSEN, published in 1910. The paper was translated from the German original into English by H. MARSHALL under the title EXOGENOUS PSYCHOSES, and included in THEMES AND VARIATIONS IN EUROPEAN PSYCHIATRY, edited by HIRSCH and SHEPHERD (1974).

[37] In his classic paper, Bonhoeffer (1909) identified the clinical manifestations in which exogenous psychosis becomes manifest as follows: "The forms which these exogenous psychotic reactions take are first, delirium, which may also more rarely appear in modified guise with hallucinosis as the dominant clinical feature. Next come the epileptiform reactions, which may present as states of anxious or frenzied motor excitement, or alternatively, as quiet affectless twilight states. Then there are the various kinds of stupor, and lastly, confusional states, which may show hallucinatory, catatonic or dissociative features". He noted that there are also atypical exogenous psychotic reactions which are displayed as "dysthymic syndrome", "hallucinatory reaction", "paranoid reaction", or "schizophreniform reaction". Because of these atypical forms, "a complete distinction between the symptomatology of the exogenous clinical pictures and that of the psychoses which are regarded as endogenous cannot be maintained". Bonhoeffer believed that only people with a particular predisposition (Predilektionstypus) would develop exogenous psychosis. In this monograph, the atypical forms of exogenous psychoses are conceptualized as patterns of sui generis psychiatric disorders which are transiently released by an acute biologic trauma.

(including infectious diseases and toxic agents), which is detectable by physical and/or laboratory methods.[38]

In subsequent years, the diagnostic concept of exogenous psychosis, i.e., mental illness, which (in the most typical cases) is characterized by the simultaneous presence of delirium[39] and physical illness, has received substantial support. It was also recognized, that in terms of its etiology, the symptom display of exogenous psychosis, is nonspecific.[40] Because of this, exogenous psychosis, a diagnostic concept, does not qualify for a distinctive nosologic category. It is a set of syndromes, which indicate that

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[38] There is no consensus with regard to the importance of Bonhoeffer's work in the development of the diagnostic concept of "exogenous psychosis". BERRIOS (1981), in his paper DELIRIUM AND CONFUSION IN THE 19TH CENTURY: A CONCEPTUAL HISTORY, maintained that Bonhoeffer's contributions are overrated. According to him, the crucial concepts relevant to organic states had been sorted out by the end of the 19th century in BRIERRE's (1845) influential essay, DE DELIRE AIGU, and in the entries on delirium by POWER and SEDWICK (1892), in THE NEW SYDENHAM'S SOCIETY'S LEXICON OF MEDICINE AND ALLIED SCIENCES, and in TUKE's (1892) DICTIONARY OF PSYCHOLOGICAL MEDICINE. Berrios considered REDLICH's (1912) monograph, DIE PSYCHOSEN BEI GEHIRNKRANKUNGEN, "far more impressive" than BONHOEFFER's (1910) monograph, DIE SYMPTOMATISCHEN PSYCHOSEN.

[39] In delirium, within the frame of reference of general psychopathology, the experiencing of "psychic life" as a "momentary whole" is affected. Because of this, Jaspers (1962) discussed delirium under "subjective phenomena of morbid psychic life", or "phenomenology".

[40] Bonhoeffer (1909) recognised that <u>exogenous psychoses</u> are non-specific in terms of their etiology. Because of this, he maintained that "there is no need to consider the special symptomatology encountered in the different reactions." He emphasized, that "although they may appear more frequently in association with one or another organic condition mentioned, they can be found occurring after any of them". Therefore, according to him "no useful purpose would be served by differentiating etiologically between the symptoms which follow, say, fever, exhaustion, or autointoxication".

a physical disease or toxic agent, by having a transient effect on the brain, has produced reversible neurophysiologic changes.

Current Classifications

ICD-9

In the 1975 (Ninth) Revision of the International Classification of Diseases of the World Health Organization, mental disorders are divided into three major classes of illness[41]; and within the class of psychoses, the somatically determined psychoses, referred to as organic psychotic conditions[42], are one of the two major categories of disorders.[43]

In the ICD-9, the diagnostic importance of dementia[44] and delirium[45] are explicitly recognized. Nevertheless, the distinctiveness between organic psychoses, i.e., disorders in which the dementia

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[41] The three major classes of illness in the ICD-9 are: (1) psychoses, (2) neurotic disorders, personality disorders and other nonpsychotic mental disorders and (3) mental retardation.

[42] In the ICD-9, organic psychotic conditions are defined as follows: "Syndromes in which there is impairment of orientation, memory, comprehension, calculation, learning capacity and judgment." In addition to these essential features, "there may also be shallowness or lability of affect, or a more persistent disturbance of mood, lowering of ethical standards and exaggeration or emergence of personality traits, and diminished capacity for independent decision."

[43] In the ICD-9, the class of psychoses includes two major categories of disorders, i.e., organic psychotic conditions and other psychoses.

[44] In the ICD-9, the term, dementia, refers to organic psychosis which is "chronic or progressive" and which, "if untreated, is usually irreversible and terminal".

[45] In the ICD-9, the term, delirium, refers to organic psychosis with a short course in which the features of dementia are "overshadowed by clouded consciousness, confusion, disorientation, delusions, illusions and often vivid hallucinations".

syndrome is linked with neuropathologic changes, and exogenous psychoses, i.e., disorders in which delirium is linked with physical illness, is not used as an organizing principle in the classification of these illnesses. As a result, alcoholic psychoses, one of the five subcategories of organic psychotic conditions, include both, i.e., organic psychoses (such as alcoholic Korsakoff's psychosis and other alcoholic dementia) and exogenous psychoses (such as delirium tremens and other alcoholic hallucinosis) (Table I).

DSM-III

In the Third Edition of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association, mental disorders are divided into 15 clinical syndromes.[46] One of these syndromes is somatically determined psychoses, referred to as

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[46] In the DSM-III, mental disorders are separated into clinical syndromes, described in Axis I, and personality disorders, described in Axis II. The 15 clinical syndromes of Axis I are as follows: (1) disorders usually first evident in infancy, childhood or adolescence, (2) organic mental disorders, (3) substance use disorders, (4) schizophrenic disorders, (5) paranoid disorders, (6) psychotic disorders not elsewhere classified, (7) affective disorders, (8) anxiety disorders, (9) somatoform disorders, (10) dissociative disorders, (11) psychosexual disorders, (12) factitious disorders, (13) disorders of impulse control not elsewhere classified, (14) adjustment disorders, and (15) psychological factors affecting physical condition.

Table I

SENILE AND PRESENILE ORGANIC PSYCHOTIC CONDITIONS
- Senile dementia, simple type
- Presenile dementia
- Senile dementia, depressed or paranoid type
- Senile dementia with acute confusional state
- Arteriosclerotic dementia
- Other
- Unspecified

ALCOHOLIC PSYCHOSES
- Delirium tremens
- Korsakov's psychosis, alcoholic
- Other alcoholic dementia
- Other alcoholic hallucinosis
- Pathological drunkenness
- Alcoholic jealousy
- Other
- Unspecified

DRUG PSYCHOSES
- Drug withdrawal syndrome
- Paranoid and/or hallucinatory states induced by drugs
- Pathological drug intoxication
- Other
- Unspecified

TRANSIENT ORGANIC PSYCHOTIC CONDITIONS
- Acute confusional state
- Subacute confusional state
- Other
- Unspecified

OTHER ORGANIC PSYCHOTIC CONDITIONS (CHRONIC)
- Korsakov's psychosis or syndrome (nonalcoholic)
- Dementia in conditions classified elsewhere
- Other
- Unspecified

Classification of organic psychotic conditions in the ICD-9.

organic mental disorders."[47]

The two categories of disorders within organic mental disorders in the DSM-III are: (1) organic mental disorders whose etiology or psychophysiological process is listed in the mental disorders section of the ICD-9-CM,[48] and (2) organic brain syndromes,[49] whose etiology or pathophysiological process is listed in the somatic disorders section of the ICD-9-CM (or is unknown).

By separating organic brain syndromes which are intrisically

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[47] In the DSM-III, "the essential feature of organic mental disorders is a psychological abnormality associated with transient or permanent dysfunction of the brain. They are diagnosed (a) by recognizing the presence of one of the organic brain syndromes, and (b) by demonstrating by means of the history, physical examination, or laboratory tests, the presence of a specific organic factor judged to be etiologically related to the abnormal mental state. Under certain circumstances, however, a reasonable inference of an organic factor can be made from the clinical features alone..."

[48] ICD-9-CM stands for the Clinical Modification of ICD-9. The clinical modification was prepared at the request of physicians in the United States, who "found that they needed a classification with more specificity than provided by the ICD-9".

[49] Under the heading of organic mental disorders in the DSM-III, disorders are separated from syndromes. Included under organic brain syndromes are: (1) delirium and dementia in which cognitive impairment is relatively global, (2) amnestic syndromes and organic hallucinosis in which relatively selective areas of cognition are impaired, (3) organic delusional syndromes and organic affective syndromes which have features resembling schizophrenia or affective disorders, (4) organic personality syndrome in which personality is affected, (5) intoxication and withdrawal in which the disorder is associated with ingestion or reduction in use of a substance and does not meet the criteria for any of the other syndromes, and (6) atypical or mixed organic brain syndrome not classifiable otherwise.

linked to somatic illness, from the other organic mental disorders, i.e., dementias arising in the senium and presenium, and substance-induced, the DSM-III has set the stage for the recognition of the dichotomy between organic and exogenous psychoses. However, as the result of a shift in emphasis in the classification of these disorders to etiology and phenotypic manifestations,[90] and from the typical to the atypical forms of presentation in Bonhoeffer's (1909) classification,[91] the traditional diagnostic concepts of organic and exogenous psychoses are dismissed (Table II).

DSM-III-R

The Revised Third Edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (1987) shows little difference from the DSM-III.[92] In variance with the DSM-III, however, it divides organic mental disorders into three,

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[90] The two distinctive clinical syndromes of organic psychosis in the DSM-III, are the dementia syndrome and the amnestic syndrome. However, in the different disorders the emphasis is not on these syndromes, but on the phenotypic manifestations, such as delirium, delusions and/or depression.

[91] There is only one typical (i.e., delirium), whereas there are three atypical forms (i.e., delusional, hallucinatory and affective) of Bonhoeffer's (1909) exogenous psychoses included in the DSM-III-R.

[92] The DSM-III-R includes one more category of disorders than the DSM-III. The added category is sleep disorders.

Table II

ORGANIC MENTAL DISORDERS WHOSE ETIOLOGY OR PATHOPHYSIOLOGICAL PROCESS IS A DISORDER LISTED IN THE MENTAL DISORDER SECTION OF ICD-9-CM

Dementias Arising in the Senium and Presenium
- Primary degenerative dementia, senile onset,
  - with delirium
  - with delusions
  - with depression
  - uncomplicated
- Primary degenerative dementia, presenile onset
  - with delirium
  - with delusions
  - with depression
  - uncomplicated
- Multi-infarct dementia
  - with delirium
  - with delusions
  - with depression
  - uncomplicated

Substance Induced
- Alcohol
  - intoxication
  - idiosyncratic intoxication
  - withdrawal
  - withdrawal delirium
  - hallucinosis
  - amnestic disorder
  - dementia associated with alcoholism
    - with delirium
    - with delusions
    - with depression
    - uncomplicated
- Barbiturate or similarly acting sedative or hypnotic
  - intoxication
  - withdrawal
  - withdrawal delirium
  - amnestic disorder
- Opioid
  - intoxication
  - withdrawal
- Cocaine
  - intoxication
- Amphetamine or similarly acting sympathomimetic
  - intoxication
  - delirium
  - delusional disorder
  - withdrawal
- Phencyclidine (PCP) or similarly acting arylcyclohexylamine abuse
  - intoxication
  - delirium
  - mixed organic mental disorder
- Hallucinogen
  - hallucinosis
  - delusional disorder
  - affective disorder
- Cannabis
  - intoxication
  - delusional disorder
- Tobacco
  - withdrawal
- Caffeine
  - intoxication
- Other or unspecified substance
  - intoxication
  - withdrawal
  - delirium
  - dementia
  - amnestic disorder
  - delusional disorder
  - hallucinosis
  - affective disorder
  - personality disorder
  - atypical or mixed organic mental disorder

ORGANIC MENTAL DISORDERS WHOSE ETIOLOGY OR PATHOPHYSIOLOGICAL PROCESS IS A DISORDER LISTED IN THE SOMATIC DISORDERS SECTION OF ICD-9-CM
- delirium
- dementia
- amnestic syndrome
- organic delusional syndrome
- organic hallucinosis
- organic affective syndrome
- organic personality syndrome
- atypical or mixed organic brain syndrome

Classification of organic mental disorders in the DSM-III.

instead of two sections,[83] and separates primary degenerative dementia of the Alzheimer type from senile dementia not otherwise specified[84] (Table III).

ICD-10

In the ICD-10 mental disorders are divided into ten categories of illness.[85] One of the categories is somatically determined

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[83] In contradistinction to the DSM-III, in the DSM-III-R, organic mental disorders are divided into three sections, i.e., dementia arising in the senium and presenium, psychoactive substance-induced organic mental disorders, and organic mental disorders associated with physical disorders or conditions, or whose etiology is unknown.

[84] The diagnosis of primary degenerative dementia of the Alzheimer type with senile or presenile onset in the DSM-III-R is a considerably broader diagnostic concept, than the diagnostic concept of Alzheimer's disease, a presenile dementia described in 1907. Common neuropathologic characteristics of both are senile plaques and their amyloid as well as neurofibrillary tangles and paired helical filaments of the "tau" species of proteins in the brain. However, the possible marker for the Alzheimer's gene on chromosone 21, the same chromosome that is involved in Down's syndrome, applies only to Alzheimer's disease (Heston and Mastri, 1977; Heston, 1984; Cutler et al., 1985; Van Broeckhoven et al., 1987, 1990; St. George-Hyslop et al., 1987; Goate et al., 1989.) It should be noted that in the studies of Pericak-Vance et al. (1988), and Schellenberg, Bird and Wijsman (1988), the chromosome 21 linkage could not be confirmed.

[85] The ten categories of mental disorders of the ICD-10 include: (1) organic, including symptomatic mental disorders, (2) mental and behavioral disorders due to psychoactive substance use, (3) schizophrenia, schizotypal and delusional disorders, (4) mood (affective) disorders, (5) neurotic, stress-related, and somatoform disorders, (6) behavioral syndromes associated with physiological disturbances or physical factors, (7) disorders of adult personality and behaviour, (8) mental retardation, (9) disorders of psychological development, and (10) behavioral and emotional disorders with onset usually occurring in childhood or adolescence.

Table III

DEMENTIAS ARISING IN THE SENIUM AND PRESENIUM

- Primary Degenerative Dementia of the Alzheimer Type, Senile Onset
  - with delirium
  - with delusions
  - with depression
  - uncomplicated
- Primary Degenerative Dementia of the Alzheimer's Type, Presenile Onset
  - with delirium
  - with delusions
  - with depression
  - uncomplicated
- Multi-infarct Dementia
  - with delirium
  - with delusions
  - with depression
  - uncomplicated
- Senile Dementia Not Otherwise Specified
- Presenile Dementia Not Otherwise Specified

PSYCHOACTIVE SUBSTANCE-INDUCED ORGANIC MENTAL DISORDERS

Alcohol	intoxication
	idiosyncratic intoxication
	uncomplicated alcohol withdrawal
	withdrawal delirium
	hallucinosis
	amnestic disorder
	dementia associated with alcoholism
Amphetamine or Similarly Acting Sympathominetic	intoxication
	withdrawal
	delirium
	delusional disorder
Caffein	intoxication
Cannabis	intoxication
	delusional disorder
Cocaine	intoxication
	withdrawal
	delirium
	delusional disorder
Hallucinogen	hallucinosis
	delusional disorder
	mood disorder
	posthallucinogen personality disorder
Inhalent	intoxication
Nicotine	withdrawal
Opiod	intoxication
	withdrawal
Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine	intoxication
	delirium
	delusional disorder
	mood disorder
	organic mental disorder NOS
Sedative, Hypnotic or Anxiolytic	intoxication
	uncomplicated withdrawal
	withdrawal delirium
	amnestic disorder
Other or Unspecified Psychoactive Substance	intoxication
	withdrawal
	delirium
	dementia
	amnestic disorder
	delusional disorder
	hallucinosis
	mood disorder
	anxiety disorder
	personality disorder
	organic mental disorder

ORGANIC MENTAL DISORDERS ASSOCIATED WITH PHYSICAL DISORDERS OR CONDITIONS WHOSE ETIOLOGY IS UNKNOWN

- delirium
- dementia
- amnestic disorder
- organic delusional disorder
- organic hallucinosis
- organic mood disorder
  - manic
  - depressed
  - mixed
- organic anxiety disorder
- organic personality disorder
  - explosive type
- organic mental disorder NOS

Classification of organic mental disorders in the DSM-III-R (Differences from DSM-III are underlined).

psychoses, referred to as organic, including symptomatic, mental disorders.

The ICD-10 represents an important step in the classification of organic, including symptomatic, mental disorders. It is the first classification which separates: (1) the organic psychoses from the exogenous psychoses, (2) the psychoses with the dementia syndrome, from the psychoses with the amnestic syndrome within the organic psychoses, and (3) the typical forms of exogenous psychoses (i.e., delirium, other than induced by alcohol or drugs) from the atypical forms of exogenous psychoses, referred to as symptomatic psychoses (i.e., other mental disorders due to brain disease, damage or dysfunction, or to physical disease including hormonal disturbances) (Table IV)[96].

Although organic psychoses are separated from exogenous psychoses in the ICD-10, both, organic and exogenous psychoses are included under the category of organic, including symptomatic, mental

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[96] The subcategory, delirium other than induced by alcohol or drugs, is restricted to delirium and therefore does not completely overlap with, and includes all of Bonhoeffer's (1909) typical forms of exogenous psychoses; whereas the subcategory, other mental disorders, due to brain disease, damage or dysfunction, or to physical disease, including hormonal disturbances, includes also some of the typical forms of exogenous psychoses, and therefore does not completely overlap with the atypical forms of Bonhoeffer's exogenous psychoses. Considering that each of the different forms of disorders included in this category correspond with patterns displayed by one or another sui generis psychiatric disorder, the disorders of this subcategory are referred to as symptomatic psychoses and/or symptomatic psychiatric disorders.

Table IV

ICD-10 ORGANIC PSYCHOSES	EXOGENOUS PSYCHOSES	
	Typical Form	Atypical Form (Symptomatic Psychoses)
I. 1. Dementia in Alzheimer's disease 2. Vascular dementia 3. Dementia in diseases classified elsewhere 4. Dementia unspecified II. 1. Organic amnestic syndrome, other than induced by alcohol or drugs	I. 1. Delirium other than induced by alcohol or drugs	II. 1. Other mental disorders, due to brain disease, or, damage or dysfunction or to physical disease including hormonal disturbances a. organic hallucinosis b. organic catatonic disorder stupor excitement c. organic delusional or schizophrenia-like disorder d. organic affective disorder manic bipolar depressive e. organic anxiety disorder f. organic dissociative disorder g. organic emotionally labile or asthenic disorder

Schematic presentation of relationship between the ICD-10 classification of organic, including symptomatic, mental disorders and the traditional classification of somatically determined psychoses.

disorders (Table V)."[99] On the other hand, mental and behavioral disorders due to psychoactive substance use are assigned a separate category of mental disorders (Table VI).

Psychopharmacologic Considerations

The primary treatment modality of somatically determined psychoses, is causal treatment, if the etiology can be identified. However, causal treatment of the somatic illness, may need to be supplemented, with the administration of psychotropic drugs for the control of the released psychopathologic symptoms.

Among the different psychotropic medications antipsychotic-neuroleptics, and especially haloperidol (a butyrophenone)[100], are extensively employed (Kaplan and Sadock, 1988). There is no conclusive evidence, however, that in the treatment of psychotic manifestations in the somatically determined psychoses, the effectiveness of any of the neuroleptics would be superior (to the others). Furthermore, there are indications that in the treatment of anxiety manifestations in the exogenous psychoses, anxiolytic-benzodiazepines are comparable to antipsychotic-neuroleptics in

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[99] In Part Two of this series, organic and exogenous psychoses will be separated from each other and organic psychoses will be discussed in the monograph on neuropsychiatric disorders, whereas exogenous psychoses will be discussed in the monograph on sui generis psychiatric disorders.

[100] Haloperidol is the chlorpromazine analogue of the butyrophenone series. It is an antipsychotic-neuroleptic, developed by Janssen and his collaborators (1959).

Table V

DEMENTIA IN ALZHEIMER'S DISEASE
predominantly
delusional
hallucinatory
depressed
mixed
with early onset (Type 2)
with late onset (Type 1)
atypical or mixed
VASCULAR DEMENTIA
predominantly
delusional
hallucinatory
depressed
mixed
of acute onset
multi-infarct (predominantly cortical)
subcortical
mixed cortical and subcortical
other
DEMENTIA IN DISEASES CLASSIFIED ELSEWHERE
predominantly
delusional
hallucinatory
depressed
mixed
in Pick's disease
in Creutzfeldt-Jakob disease
in Huntington's disease
in Parkinson's disease
in human immunodeficiency virus disease
in other diseases classified elsewhere

ORGANIC AMNESIC SYNDROME OTHER THAN
INDUCED BY ALCOHOL OR DRUGS
DELIRIUM OTHER THAN INDUCED BY ALCOHOL
OR DRUGS
not superimposed on dementia
superimposed on dementia
other
OTHER MENTAL DISORDERS, DUE TO BRAIN
DISEASE, DAMAGE OR DYSFUNCTION, OR TO
PHYSICAL DISEASE, INCLUDING HORMONAL
DISTURBANCE
organic hallucinosis
organic catatonic disorder (stupor or excitement)
organic delusional or schizophrenia-like disorder
organic affective disorder
manic
bipolar
depressive
organic anxiety disorder
organic dissociative disorder
organic emotionally labile or asthenic disorder
other
PERSONALITY AND BEHAVIORAL DISORDER
DUE TO BRAIN DISEASE, DAMAGE, OR
DYSFUNCTION
organic personality disorder
postencephalitic syndrome
other
subcortical
postconcussional syndrome
other

Classification of organic, including symptomatic, mental disorders in the ICD-10.

Table VI

DISORDERS RESULTING FROM USE OF
ALCOHOL
TOBACCO
OPIOIDS
CANNABINOIDS
SEDATIVES OR HYPNOTICS
COCAINE
OTHER STIMULANTS
HALLUCINOGENS
VOLATILE SOLVENTS
MULTIPLE DRUG USE AND
USE OF OTHER PSYCHOACTIVE SUBSTANCES

- Acute Intoxication
  - uncomplicated
  - with trauma or other bodily injury
  - with other medical complications
  - with delirium
  - with perceptual distortion
  - with coma
  - with convulsions
- Harmful Use
  - mild
  - moderate
  - severe
- Dependence Syndrome
  - currently abstinent
  - currently abstinent but in a protected environment
  - currently on a clinically supervised maintenance regime
  - currently using the substance
  - continuous use
  - episodic use
- Withdrawal State
  - uncomplicated
  - with convulsions
- Withdrawal State With Delirium
  - without convulsions
  - with convulsions
- Psychotic Disorder
  - schizophrenia-like
  - predominantly delusional
  - predominantly hallucinatory
  - predominantly polymorphic
  - predominantly depressive symptoms
  - predominantly manic symptoms
  - mixed
- Alcohol or Drug Induced Amnestic Syndrome
- Alcohol or Drug Induced Residual and Late Onset Psychotic Disorder
  - flashbacks
  - personality or behavioral disorder
  - residual affective disorder
  - dementia
  - other persisting cognitive impairment
  - late onset psychotic disorder
- Other Mental and Behavioral Disorders Induced by Alcohol or Drugs

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Classification of mental and behavioral disorders due to psychoactive substance use in the ICD-10.

their therapeutic effectiveness (Wells and McEvoy, 1982).[59]

Structurally Determined Psychoses

Structurally determined psychoses, in variance with somatically determined psychoses, are characterized by distinctive psychopathologic syndromes in the absence of physical illness. Each disorder (psychosis) evolves, in a predictable-stereotypic manner, and becomes manifest in a structure, generated by the onset, course and outcome of the psychopathologic symptoms displayed in the cross-sectional clinical picture.

Etiology Based Diagnoses

In spite of the absence of etiologic knowledge, structurally determined psychoses are divided into reactive and endogenous. Within the frame of reference of this dichotomy, the diagnosis, endogenous (also referred to as autochthonous) refers to psychoses which assumedly arise from inner causes.[60] The term, implies an

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[59] In 1967 the World Health Organization introduced the term anxiolytic sedative, for substances which can reduce pathologic anxiety, tension and agitation without therapeutic effects on cognitive and perceptual processes. Today the most extensively employed anxiolytic sedatives are from the class of benzodiazepines. The findings that anxiolytic benzodiazepines are comparable in their therapeutic effects to antipsychotic-neuroleptics in delirium have important heuristic implications, because the action mechanism of benzodiazepines is distinctly different from the action mechanism of neuroleptics.

[60] GOODWIN (1989) in his Foreword to PSYCHIATRIC DIAGNOSIS (by GOODWIN and GUZE) pointed out that diagnostic terms, such as endogenous, autochthonous, psychogenic, reactive, etc., are "involved by physicians to explain the unexplained". Regardless, "people continue to speculate about etiology, of course, and this is good if it produces testable hypotheses, and bad if the speculation is mistaken for truth".

innate-genetic biologic defect (Morel, 1857),[61] or, if one accepts the "endogeny theory" of Moebius (1893),[62] a "constitutionally determined predisposition". On the other hand, the concept of reactive (also referred to as psychogenic) refers to psychoses which arise assumedly from conflictual experiences and/or stressful life events.[63] However, in the absence of distinctive clinical features between the two categories of disorders, the concepts of endogenous and reactive psychoses have not yielded testable nosologic hypotheses.

Structurally Based Diagnoses

Attempts to identify and classify disorders within the

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[61] MOREL's (1857) concept of an innate biologic defect was first presented in his TRAITÉ DES DÉGENERESCENCES PHYSIQUES, INTELLECTUELLES ET MORALES DE L'ESPÈCE HUMAINE. In his monograph on A CENTURY OF PSYCHIATRY, published in 1983, PIERRE PICHOT summed up Morel's concept of degeneration as follows: "From the two principles, namely, the production of pathological variations by pathogenic environmental conditions and the transmission of inherited characteristics, Morel logically deduced that these degenerative hereditary strains would become progressively worse in lineal descent since the continued existence of the causes could not fail to aggravate their severity in successive generations...For Morel, mental disorders were, in many cases, nothing but a pre-eminent expression of degeneration...the specific clinical manifestations corresponding to the level of degeneration affecting the individual presenting them".

[62] The endogeny theory was presented by MOEBIUS in 1893 in his ABRISS DER LEHRE VON NERVENKRANKHEITEN; and subsequently in 1900 in his monograph on DEGENERATION. In their DIAGNOSTIC CRITERIA FOR SCHIZOPHRENIC AND AFFECTIVE PSYCHOSES, published in 1983, BERNER ET AL. considered Moebius' endogeny hypothesis as one of the most important theoretical concepts relevant to the formulation of diagnostic criteria for endogenous psychoses.

[63] The concept of reactive psychosis is restricted to psychoses which are assumedly the result of psychogenic trauma because the term exogenous is reserved for psychoses which are the result of biologic trauma.

structurally determined psychoses began with a purely descriptive phase in which clinical research was restricted to "collecting, recording, and faithfully portraying phenomena as they were encountered". In the absence of an organizing principle the descriptive observations yielded "individual psychoses" in which, according to Birnbaum (1923), "each psychosis was unique and occurred only in the particular form displayed."

The initial approach "has been concerned first and foremost with describing and recording clinical phenomena from direct observation of patients, and with delineating individual symptoms and the course of the symptoms encountered." However, "by ordering and grouping its data in an exact, systematic and comprehensive manner, it had done more; it has amassed a firm body of clear clinical syndromes and an equally firm body of clinical phenomena which recur in the regular, discrete form and sequence that is usually expected of specific disease categories" (Birnbaum, 1923)[4]

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[4] The origin of the structural approach to psychiatric nosology is in Birnbaum's (1923) monograph, DER AUFBAU DER PSYCHOSE. According to him "with the passage of time, descriptive research has not escaped the fate which finally befalls it in all scientific discipline: when too much material has been recorded and arranged further research tends to choke on the surfeit of data that have been amassed". To break the impasse created by the excess of data Birnbaum developed a new methodology, he referred to as "structural analysis", which "by studying the tectonic relationships between symptoms allows one to arrange them according to their hierarchical significance, their clinical importance and their significance in regard to the category of illness involved." He believed that "in the sphere of nosology, or systematic psychiatry, structural analysis (by organizing the material around five factors, i.e., predisposing, preforming, pathogenetic, provoking and pathoplastic) paves the way for a schematic arrangement which is clinically beyond reproach and which distinguishes those features which are important, specific and caused by illness, from those which are incidental, non-specific accompaniments; and thereby establishes the decisive nosological factors in question". The first two chapters of Birnbaum's monograph were translated from the German original into English by H. MARSHALL under the title THE MAKING OF A PSYCHOSIS: THE PRINCIPLES OF STRUCTURAL ANALYSIS IN PSYCHIATRY, and are included in THEMES AND VARIATIONS IN EUROPEAN PSYCHIATRY, edited by HIRSCH and SHEPHERD (1974).

Course and Outcome

The first organizing principle for the detection and classification of nosologic categories within structurally determined psychoses was based on the course[“] and the outcome of illness. By developing a clinical methodology for the assessment of variables relevant to course and outcome, and by employing the new methodology, KRAEPELIN (1896), in the fifth edition of his LEHRBUCH DER PSYCHIATRIE, identified and separated two major psychiatric disorders from the multitude of clinical syndromes[“]. One of these two syndromes, which in terms of course and outcome, was episodic and remitting, he referred to as manic depressive

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[“] It should be noted that already in 1838 "Esquirol emphasized age at onset and course of illness as valuable additions to cross-sectional descriptive definition" (Frances et al., 1990).

[“] Kahlbaum's (1874) conceptual framework and especially his postulation of a close correspondance between etiology, brain pathology, symptom pattern and outcome picture, had a decisive influence on Kraepelin's (1896) work, and especially his shift of emphasis from clinical syndromes to the progression of disease. To focus attention on his shift of emphasis, Kraepelin, in the Introduction to the fifth edition of his textbook, wrote: "In the development of the present work, the current edition represents the last decisive step which goes from the symptomatic conception to the clinical conception of insanity. This change in point of view, the necessity of which has been brought home to me more and more forcibly by practical needs, is mainly characterized by the delineation and grouping of pathologic pictures. Everywhere the importance of the external signs has had to yield place to the criteria which derive from the developmental conditions, the course and the issue of the individual disorders. All the pure syndromes have disappeared from the nosology" (Pichot, 1983).

insanity,[67] and the other one, which in terms of course and outcome was continuous and progressing, he referred to as dementia praecox[68]. Kraepelin's original nosologic concept of manic depressive insanity embraced "the whole domain of the so called periodic or circular insanities", including the "morbid states termed melancholia" and mania, and a considerable proportion of the amentias.[69] Similarly, Kraepelin's (1899) original nosologic concept of dementia praecox embraced the whole domain of insanities

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[67] In the first edition of his textbook, Kraepelin (1883) described six different forms of melancholia, i.e., simple, gravis, stuporous, paranoid, fantastic and delirious, and four different forms of mixed states, i.e., depressed mania, agitated depression, depression with flight of ideas, and depression with partial inhibition. In his 1896 presentation he contended that all these different forms are manifestation of one and the same nosologic entity, i.e., manic depressive insanity. Subsequently, in the eighth edition, he characterized the disorder by "distinctive episodes (which are) more or less sharply delineated from each other or from health" and "may or may not resemble each other" to the extent that they "often represent antithetical pictures".

[68] Kraepelin (1893), in the fourth edition of his textbook, brought together the syndromes of hebephrenia, described by Hecker (1871) with consideration to Kahlbaum's (1863) diagnostic concept of "paraphrenia hebetica", catatonia or tension insanity, described by Kahlbaum (1874), and dementia paranoides under the heading psychic degeneration processes. Subsequently in the fifth edition, he characterized this "group of clinical conditions" by its "peculiar destruction of internal connections of the personality and a marked damage of emotional and volitional life".

[69] Kraepelin's (1896) already broad original definition of manic depressive insanity was later on expanded to include "all cases of affective excess", and ultimately, on the basis of the contributions of Dreyfus (1905), also involutional melancholia, a disorder which at the beginning, he regarded as a separate nosological entity, because of its prolonged course.

which progressed towards "psychic enfeeblement".[78]

Polarity and Phenomenology

The second organizing principle for the detection and classification of valid nosologic categories within structurally determined psychoses was based on polarity and phenomenology. By developing a clinical methodology for the assessment of variables

[78] Kraepelin's (1899) already broad original definition of dementia praecox was expanded in the seventh edition of his textbook to include Magnan's (1891-1892, 1893) diagnostic concept of delire chronique. However, in the eighth edition he separated the paranoid forms of dementia praecox from the paranoid deteriorations (in which emotions and volition remained intact). In the eighth edition, Kraepelin (1909-1915) put forward a completely new classification in which he distinguished among ten different forms of dementia praecox including Diem's (1903) dementia simplex, silly deterioration (replacing the term hebephrenia), depressive deterioration, depressive deterioration with delusional formation, circular, agitated, periodic, catatonic, and paranoid forms, and schizophasia. Kraepelin's (1904) textbook was abstracted and adapted from the seventh German edition into English by A. ROSS DIEFENDORF, under the title CLINICAL PSYCHIATRY: A TEXT-BOOK FOR STUDENTS AND PHYSICIANS. The English edition was published in 1907 by the Macmillan Company in New York and London.

relevant to polarity[71] and phenomenology[72], LEONHARD (1957) undertook the task of re-evaluating Kraepelin's (1899)

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[71] In defining polarity in his monograph, The Classification of Endogenous Psychoses, Leonhard (1979) wrote: "The bipolar form (of illness) displays a considerably more colorful appearance; it varies not only between the two poles, but in each phase offers different pictures. The unipolar forms of which there are several, return in a periodic course, with the same symptomatology. Every individual form is characterized by a syndrome associated with no other form and not even related transitionally to any other forms. On the other hand, in bipolar cases, no clear syndromes can be described since there are many transitions between various formations and the picture may even be distorted during one phase. Thus, one can generally recognize a bipolar form during the first phase. In the same sense, one is also in the position to recognize as bipolar those forms which only accidentally swing toward one pole but which contain the potential toward the other pole. Consequently the differentiation is better made between polymorphic (bipolar) and pure (unipolar) forms". On the basis of this original definition, the concept of "bipolar" refers primarily to a multiform (polymorphic) - continuously changing clinical picture and only secondarily to the potential to display both mood extremes, i.e., hyperthymia, i.e., elation or mania, and dysthymia, i.e., sadness or depression; and the concept of "monopolar" or "unipolar" refers primarily to a simple (monomorph) - consistently the same clinical picture and only secondarily to the restricted potential to display only one or another mood, extreme, i.e., hyperthymia or dysthymia. Furthermore, within Leonhard's frame of reference, polarity is not restricted to mood, as in manic-depressive insanity, but extends to emotions in anxiety-happiness, one of the forms of cycloid psychosis, and to activity in periodic catatonia, one of the forms of unsystematic schizophrenia.

[72] Leonhard's (1957) different subforms of disease were derived by a careful analysis of the phenomenology of the disorders, essentially on the basis of the principles set out by Jaspers (1913) in his General Psychopathology. As it will be discussed in Part Two in the Classification of Sui Generis Psychiatric Disorders, Leonhard combined Jaspers' phenomenology with Wernicke's (1900) conceptual framework relevant to the psychic reflex. It should be noted, however, that while Leonhard adopted Jaspers' methodology, he did not share Jaspers' theoretical frame of reference. Because of this, instead of employing Jaspers' terminology--that could have been done without any difficulties--he introduced his descriptive, but somewhat idiosyncratic terms. Some believe that if this would not have happened Leonhard's work would not have been pushed aside from the main stream and would have gained much sooner, much wider acceptance.

classificatory scheme"[73]. As a result, in his AUFTEILUNG DER ENDOGENEN PSYCHOSEN"[74], he identified and separated five major groups of disorders"[75] -- consisting of 35 different clinical illnesses -- within the psychoses included by Kraepelin under manic depressive insanity and dementia praecox.

It was on the basis of polarity, that Leonhard separated within manic-depressive insanity (or affective psychoses), the unipolar phasic psychoses, from bipolar manic-depressive disease; and within dementia praecox or schizophrenia, the unipolar systematic forms of illness, from the bipolar unsystematic forms. On the other

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[73] In the Introduction to his Classification of Endogenous Psychoses, Leonhard (1979) wrote: "Kraepelin's teachings have been rejected, but whenever nosological questions are raised, his dichotomy of the endogenous psychoses reappears.....In this stance, I repeatedly observe differences among the endogenous psychoses, which are at times great, and which hardly appear bridgeable. What could a melancholy have in common with a hebephrenia? Or solely within the context of the schizophrenias, how could one unite a fantastic paraphrenia with a negativistic catatonia. Kraepelin's classification into only two forms has been damaging. He himself attempted many finer distinctions with great enthusiasm and continued open-mindedness, but his followers ignored this; they only saw the coarse division into schizophrenia, i.e., dementia praecox, and the manic-depressive disease".

[74] In his monograph, Aufteilung der Endogenen Psychosen, Leonhard (1957) used the conventional term, endogenous psychoses, for structurally determined psychoses. The monograph was translated from the fifth edition of the German original into English by RUSSELL BERMAN, under the title THE CLASSIFICATION OF ENDOGENOUS PSYCHOSES. The manuscript was edited by Eli Robins and published in 1979 by Irvington Publishers (Halsted Press Division of John Wiley & Sons) in New York, London, Sydney and Toronto. The sixth and last edition of Leonhard's monograph was published in 1986.

[75] The five groups of disorders in Leonhard's (1957) classification are : unipolar phasic psychoses, manic-depressive disease, cycloid psychoses, unsystematic schizophrenias and systematic schizophrenias. In his monograph on the Classification of Endogenous Psychoses, Leonhard included both, <u>unipolar phasic psychoses</u> and <u>manic-depressive disease</u>, under the <u>phasic psychoses</u>.

hand, it was with consideration to outcome, that he separated, within the bipolar disorders, the cycloid psychoses and manic-depressive disease, (i.e., the disorders with full remission between episodes), from the unsystematic schizophrenias (i.e., the disorders with partial remission between episodes).

Similarly, it was on the basis of the primarily affected structures in Wernicke's (1900) psychic reflex arc[76], i.e., afferent structures (such as perception and thinking), central structures (such as emotions and mood) and efferent structures (such as drive and psychomotility), that Leonhard (1957) separated within the

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[76] The term "reflex" was introduced by Descartes (1649) in his DES PASSIONS DE L'AME. It was adopted into physiology by WHYTT (1751) in his treatise ON THE VITAL AND OTHER INVOLUNTARY MOTIONS OF ANIMALS; and extended to embrace all activities, including the psychologic by SECHENOV (1866) in his REFLEXES OF THE BRAIN. "In accord with his attempt to grasp mental illness as cerebral illness...Wernicke's ideas were dominated by the notion of the psychic reflex arc, and he only accepted objective symptoms as relevant, i.e., movement (motility) including its special mode-language." However, Jaspers (1962) acknowledged that in spite of this seemingly simple model, Wernicke "subdivided movements into expressive, reactive and initiatory....., ~~contents~~ into awareness of the outside world, of one's own body and of one's personality....and distinguished delusion proper from explanatory delusion....." By doing so, regardless of contemporary criticisms, which perceived Wernicke's work as brain mythology, he has created a series of concepts, such as for example "perplexity, overvalued ideas, registration of memory...and the differentiation of autopsychic orientation within the allopsychic disorientation of delirium tremens..." which are of sufficient importance that "no scientist can afford not to study him seriously".

unipolar phasic psychoses, complete, and incomplete forms"; and within each, the cycloid psychoses, the unsystematic schizophrenias, and the systematic schizophrenias, three distinctive forms."[] On the other hand, it was with consideration to Jaspers' (1913) phenomenology, that Leonhard (1957) separated the cycloid psychoses from manic depressive disease", and distinguished among five subforms within each, the pure euphorias

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" In his Introduction to the chapters on The Pure Depressions and on The Pure Euphorias (in The Classification of Endogenous Psychoses), Leonhard (1957) wrote: "Pure melancholy and pure mania do not represent purely affective diseases; thought and desire are also disturbed. There are, however also psychoses in which only the emotional side becomes diseased, although not in its totality, but only on a certain level. In any case, that is how I interpret the pure depressions and the pure euphorias." The term, complete in reference to pure melancholy and pure mania, and incomplete, in reference to pure depressions and pure euphorias, was first used by PETHO ET AL. (1984) in the KDK BUDAPEST, published in the Hungarian periodical, Ideggyogyaszati Szemle.

" In Leonhard's (1957) classification, disorders with primary afferent structure involvement are confusion psychosis, a form of cycloid psychosis, cataphasia, a form of unsystematic schizophrenia, and the paraphrenias, a category of the systematic schizophrenias. Disorders with primarily central structure involvement are respectively anxiety-happiness psychosis, affect-laden paraphrenia and the hebephrenias; and disorders with primarily efferent structure involvement are motility psychosis, periodic catatonia and the catatonias.

" In the DCR Budapest-Nashville cycloid psychoses are separated from affective psychoses in general, and manic-depressive psychosis in particular, by the presence of at least two symptoms from each of the following two sets of symptoms: I (1) polymorphus (fluctuating) clinical picture, (2) protopathic change of form, (3) confusion or perplexity, (4) change in the depth of emotions, (5) strong emotional involvement with content of psychopathologic symptoms, and (6) mood swings, and II (1) delusional perceptions including delusions of reference or sudden delusional ideas, (2) hallucinations, (3) thematic incoherence, (4) misidentifications, (5) quantitative changes in speech production, (6) quantitative changes in expressive movements and (7) quantitative changes in reactive movements (Petho and Ban, 1988).

and the pure depressions (Table VII); among three subforms within each, the cycloid psychoses and the unsystematic schizophrenias (Table VIII); and among 16 subforms (i.e., six paraphrenias, four hebephrenias, and six catatonias) within the systematic schizophrenias (Table IX).

Validation of Diagnoses

According to Leonhard (1979) "if one wants to prove that an endogenously appearing psychiatric picture (i.e., a structurally determined psychosis) corresponds to a separate disease form, then it must be shown that it repeatedly occurs in a similar form. It is particularly important if the same history repeats in one family, for, from that, one could deduce that the genetically same disease does in fact produce the same clinical picture".

It is generally recognised that validation of diagnostic hypotheses is one of the most important steps in the development of nosologic concepts[**]. In spite of this, there is no consensus with regard to acceptable validation criteria for

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[**] The importance of validation studies cannot be overemphasized, because, "what the creative eyes of outstanding clinicians see can easily become blurred by the objective and impartial analysis of large series of unselected cases" (Hoenig, 1980). In the ultimate analysis, the validity of a diagnosis is judged by its "fruitfulness as a source of hypotheses regarding etiology, course and treatment response" and "by the extent to which the syndrome has proven to be a distinctive constellation or cluster that could be identified by others" (Roth and Barnes, 1981).

KENDLER (1990) in his paper TOWARDS A SCIENTIFIC PSYCHIATRIC NOSOLOGY underlines that "...a scientific nosology would involve the generation of hypotheses about the (reliability and) validity of competing diagnostic schemes. These hypotheses would be tested by the examination of the research data that addresses the given hypotheses to determine whether the individual hypothesis, e.g., diagnostic criteria A are more valid than diagnostic criteria B, is or is not supported by the available evidence".

Table VII

INCOMPLETE		COMPLETE	
Pure Manicias	Pure Depressions	Pure Mania	Pure Melancholy
Unproductive	Barried		
Hypochondriacal	Hypochondriacal		
Enthusiastic	Self-torturing		
Confabulatory	Suspicious		
Nonparticipatory	Nonparticipatory		

Complete and incomplete forms and subforms of unipolar phasic psychoses.

Table VIII

AFFERENT STRUCTURES		CENTRAL STRUCTURES		EFFERENT STRUCTURES	
Cycloid Psychosis	Unsystematic Schizophrenia	Cycloid Psychosis	Unsystematic Schizophrenia	Cycloid Psychosis	Unsystematic Schizophrenia
Confusion psychosis	Cataphasia	Anxiety-happiness psychosis	Affect-laden paraphrenia	Motility psychosis	Periodic catatonia

Corresponding diagnostic concepts between the cycloid psychoses and the unsystematic schizophrenias. In each pair of diagnoses a different structure of Wernicke's (1900) psychic reflex arc is primarily affected.

Table II

AFFERENT STRUCTURES Paraphrenias		CENTRAL STRUCTURES Hebephrenias		EFFERENT STRUCTURES Catatonias	
Subform	Necessary	Subform	Necessary	Subform	Necessary
Phonemic	Phonemic delusional	Autistic	Empty autism	Parakinetic	Continuous parakinesis
Hypochondriacal	Heteronom bodily hallucinations	Eccentric	Soft mannerisms	Prokinetic	Prokinesis
Confabulatory	Continuous fabulations	Shallow	Emotional impoverishment	Speech-prompt	Obedient answering
Expansive	Delusions of grandeur	Silly	Immature behavior	Speech-inactive	Oligal verbal responses
Fantastic	Mixed or scenic hallucinations			Manneristic	Hard mannerisms
Incoherent	Incoherence		Negativistic	Negativism	

The three forms and 16 subforms of systematic schizophrenias with their necessary (but not necessarily sufficient) manifestations in the DCR Budapest-Nashville (Petho and Ban, 1988). In each form of disease a different structure of Wernickes' (1900) psychic reflex arc is primarily affected.

mental illness[61].

In the following, the origin and the essential features of structurally determined psychoses will be briefly reviewed, with special emphasis on findings in validation studies.

Manic-Depressive Insanity

The origin of Kraepelin's (1896) nosologic concept of manic-depressive insanity was in the diagnostic concept of la folie circulaire, first described by Jean-Pierre Falret (1850-51) in his lectures at Salpetrière in Paris.[62] For Kraepelin, manic-depressive insanity was an all embracing diagnostic concept which included all the disorders with an episodic recurrence of manic, melancholic and mixed, i.e., (manic and melancholic)

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[61] KLERMAN and HIRSCHFELD (1981) in their chapter on CLINICAL NOSOLOGY, DIAGNOSIS AND CLASSIFICATION OF AFFECTIVE DISORDERS, included in PREVENTION AND TREATMENT OF DEPRESSION (edited by BAN ET AL.), grouped validation criteria under the following three categories: (1) antecedent variables which include familial and genetic variables, developmental and epidemiologic factors and psychosocial conditions; (2) concurrent correlates which include biologic abnormalities and psychologic and psychosocial conditions; and (3) predictive correlates which include outcome variables, duration of episode, probability of relapse and changing conditions.

The importance of external validators was first emphasized by ROBINS and GUZE (1970) in their paper on ESTABLISHMENT OF DIAGNOSTIC VALIDITY IN PSYCHIATRIC ILLNESS: ITS APPLCIATION TO SCHIZOPHRENIA. Such external validators include family history, demographic correlates, biological and psychological tests, environmental risk factors, concurrent symptoms, treatment response, diagnostic stability and course of illness (Kendler, 1990).

[62] The diagnostic concept of folie circulaire first appeared in J. P. Falret's Leçons a l'Hospice de la Salpetrière, printed in the 23-24th annual volume of Gaz. des Hop. (1850-51). Subsequently, in 1854, both, FALRET in his thesis, DE LA FOLIE CIRCULAIRE, and independently, BAILLARGER, in his paper, DE LA FOLIE A DOUBLE FORME, presented the same diagnostic concept in a more comprehensive manner.

symptoms, with full remission between episodes."[1]

Kraepelin's (1913) diagnostic criteria for manic-depressive insanity were adopted with some modifications by Leonhard (1957) in his nosologic concept of manic-depressive disease[2]; and Leonhard's diagnostic criteria for manic-depressive disease were adopted with some modifications by Perris (1974) in his diagnostic criteria of bipolar affective

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[1] Kraepelin's (1913) final formulation of manic-depressive insanity was published in the eighth edition (1909-1915) of his textbook. Kraepelin's diagnostic criteria for affective psychoses are based on this final formulation of manic-depressive insanity, in the monograph, DIAGNOSTIC CRITERIA FOR SCHIZOPHRENIC AND AFFECTIVE PSYCHOSES, of BERNER ET AL. (1983).

[2] Leonhard's (1957) diagnostic concept of manic-depressive disease was a restriction of Kraepelin's (1913) diagnostic concept of manic-depressive insanity to the bipolar form of phasic psychoses.

disorders"".

Results of family-genetic studies are in support of the contention that bipolar affective disorder is a genetically

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"" PERRIS (1974), in his presentation on THE HEURISTIC VALUE OF A DISTINCTION BETWEEN BIPOLAR AND UNIPOLAR AFFECTIVE DISORDERS, proposed that for the diagnosis of "bipolar affective disorder the occurrence of both manic and depressive episodes should be required, although these episodes do not necessarily need to be of a psychotic dimension. In the same presentation he suggested to label as probably bipolar affective disorder those disorders which are displayed by (1) depressive episodes and a possible history of slight hypomanic episodes, (2) manic episodes and a possible history of slight depressive episodes, and (3) depressive episodes and a family history of bipolar psychosis among first degree relatives. Perris' probably bipolar affective disorder was perceived as a distinctive nosologic category by Fieve and Dunner (1975) and Dunner, Gershon and Goodwin (1976), who separated within bipolar affective disorder two subforms. Within this dichotomy the term bipolar I referred to a disorder displayed by manic and depressive episodes, whereas the term bipolar II referred to a disorder displayed by hypomanic and depressive episodes. It has been suggested (Goodwin and Guze, 1989) that findings in the NIMH Collaborative Study in Affective Disorders (Andreasen et al., 1987) are in support of the contention that bipolar I and bipolar II disorders are genetically distinctive conditions, because in the families of patients with bipolar II disorder the incidence of bipolar II disorder was 8 percent, whereas the incidence of bipolar I disorder was 1 percent. To interpret these findings, however, it is important to note that the morbidity risk for manic depressive psychosis in Sweden and Denmark, was estimated as 1 percent by Stenstedt (1952); and that the incidence of manic-depressive disorder among the parents, siblings and children of patients with manic-depressive disease ranged from 9.1 to 12.8 percent in the studies of Roll and Entres (1936), Slater (1936) and Stenstedt (1952). Irrespective of the bipolar I and bipolar II dichotomy, Angst (1978) distinguished within bipolar affective disorder three subforms, i.e. a predominately manic type, a nuclear type and a predominantly depressive type. By employing Angst's trichotomy, Rihmer and Arato (1981) found differences in the distribution of blood types A and O among the three subforms.

meaningful nosologic category.[46] Mean concordance rates of "bipolar affective disorder" in "monozygotic-identical cotwins" were found to be as high as 72[47] and 76 percent[48] in the pooled data from several studies, reported idependently by Goodwin and Guze (1989) and Tsuang and Vandermey (1980). However, findings in genetic-transmission studies are inconsistent[49].

There are numerous hypotheses relevant to the "genetic-transmission" of "bipolar affective disease". In the generation of these hypotheses the adoption of the methodology referred to as

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[46] Genetically "meaningful", in relationship to "bipolar affective disorder", implies that within the population included under "bipolar affective disorder", there is at least one nosologically distinctive disease category (with a high level of probability).

[47] Goodwin and Guze's (1989) figure of 72 percent concordance rate of "bipolar affective disorder" in "identical twins" is based on pooled data from the nine twin studies reviewed by ALLEN (1976) in his paper, TWIN STUDIES AND AFFECTIVE ILLNESS.

[48] Tsuang and Vandermey's (1980) figure of 76 percent concordance rate of "bipolar affective disorder" in "identical twins" is based on pooled data from seven major studies conducted in Denmark, England, Germany, Norway and the United States. Tsuang and Vandermey also noted that concordance rate in studies with "identical-twins" ranges from 50 to 93 percent.

[49] In view of the inconsistent findings in "genetic-transmission" studies, Goodwin and Guze (1989) suggested that "the mode of genetic transmission in affective disorders is non-Mendelian and almost certainly polygenic".

linkage analysis" have played an important role.

On the basis of findings in genetic transmission studies it has been suggested that bipolar disorder is the result of (1) an autosomal dominant gene located on the X-chromosome (Slater, 1936,

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" Linkage analysis is a statistical approach to search for both, the "mode of inheritance" and for the "approximate chromosomal location of major genes predisposing to psychiatric disorders". By employing this approach "the search for disease related genes may proceed along three lines. " One of these lines is referred to as the protein/gene approach in which "when an abnormal protein is found to accompany a given illness, this presumed abnormal gene is used as a clue to the genetic lesion". An alternative line is the gene/protein approach which "begins by identifying the comparatively small area of the genome within which the disease gene lies". For this "radiolabeled probes are used to seek out complementary nucleic acid sequences" and "if one of these is a sequence consistently transmitted with the disease, i.e., 'linked' with the presumed aberrant gene", it is assumed that "the approximate chromosomal location of the gene is revealed." Finally, the third line employed in linkage analysis is the study of candidate genes, i.e., "genes believed to be implicated in pathogenesis". It is based on the assumption that "any abnormal biological feature, or 'biological marker', associated with the disease" is the result of "either an abnormal gene product or the product of a gene 'linked' (by its proximity to an actual disease gene", which then "if the genomic region that codes for this linked feature is known, it permits a more direct search for an offending gene". (Based on the paper GENETICS AND PSYCHIATRY: PAST DISCOVERIES, CURRENT DILEMMAS AND FUTURE DIRECTIONS by PARDES, KAUFMANN, PINCUS and WEST, published in 1989 in the American Journal of Psychiatry.)

GERSHON (1989) in his paper on RECENT DEVELOPMENTS IN GENETICS OF MANIC-DEPRESSIVE ILLNESS, defined "genetic linkage to an illness" as "a demonstration that within a particular pedigree or set of pedigrees, vulnerability to an illness is associated with a particular marker gene locus. The term marker gene locus is used to make it clear that, although a linkage finding definitively implies that an illness gene is nearby, the marker gene is most often not the disease gene. The chromosomal distance between the illness gene and the marker gene is measured by a recombination fraction, which is the proportion of instances within a studied pedigree where the illness is inherited independently of the marker. Where there is no linkage, the recombination fraction is 50 percent, but when there is linkage, this fraction approaches zero".

1938),"[91] (2) a gene linked with red-green color blindness located on the long arm of the X-chromosome and/or a gene linked with the blood group labelled X_g", located on the short-arm of the X-chromosome (Winokur and Tanna, 1969; Mendlewicz, Fleiss and Fieve, 1972; Fieve, Mendlewicz and Fleiss, 1973);"[92] (3) a dominant gene -- linked to the region of the insulin gene and the Harvey ras-1 oncogene, i.e., to the region containing tyrosine hydroxylase and a muscarinic cholinergic receptor gene -- located on the short-

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[91] The hypothesis that "bipolar affective disorder" is the result of an "autosomal dominant gene" located on the X-chromosome, was formulated by Slater in four subsequent papers, published in 1936 and 1938. It is a testable hypothesis, because if it is correct there should be no "pairs of fathers and sons who both have bipolar illness". Subsequently "in a study of families of 89 manic patients, Winokur (1970) found no ill father and ill son pairs". Similarly, in an "adoption study of bipolar patients", Mendlewicz and Rainer (1977) "found no ill father and ill son pairs". However as TSUANG and VANDERMEY (1980) in their monograph GENES AND THE MIND pointed out "the issues of X-linkage in mood disorder is not by any means settled. Numerous studies have found examples of ill father and ill son pairs."

[92] GERSHON ET AL (1976) in their paper, THE INHERITANCE OF AFFECTIVE DISORDERS: A REVIEW OF DATA AND OF HYPOTHESES "have raised strong arguments against the probability of mood disorder being linked to both color-blindness and the X_g blood group at the same time, citing the wide separation of their respective loci on the X-chromosome". Subsequently, 13 years later Gershon (1989) wrote: "There have been several series of pedigrees reported in which a substantial proportion was linked, but there is also a sizeable series with non-linkage (Gershon et al., 1987; Baron et al., 1987; Mendlewicz, Sevy and Brocas, 1987). On the basis of analysis of family study data, including our own data (Gershon et al., 1982) from Bethesda and those of Risch, Baron and Mendlewicz, (1986), it has been suggested that there is indeed genetic heterogeneity, and that one third to one half of all bipolar cases were linked to this region. However, in a pedigree series, which from simulation studies was large enough to have a reasonable power (about 70%) of detecting linkage even if only one quarter were linked, we in Bethesda have definitively excluded linkage".

arm of chromosome II (Egeland et al, 1987),[33] and (4) a gene linked with the histocompatibility locus antigen (HLA) complex located on chromosome 6 (Mathysse and Kidd, 1981; Weitkamp et al, 1981)[34]. However, the fact remains that replication of findings in genetic-transmission studies have invariably failed. In spite of this, there is a steadily increasing consensus, that "bipolar affective illness" is a "genetically transmitted disease"; and that the inconsistent findings in genetic transmission studies are at least in part the result of sampling error, i.e., contamination of the

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[33] Egeland et al (1987), on the basis of their study in the Amish, suggested that a dominant-gene located on the short-arm of chromosome II is responsible for the transmission of bipolar affective disease. It should be noted, however, that in two independently conducted clinical studies, Hodgkinson et al (1987) and Detera-Wadleigh et al. (1987), found no "close linkage of G-Harvey-ras-1 and the insulin gene to affective disorder" in North American pedigrees (Kelsoe et al, 1989). Nevertheless, subsequently Leboyer et al. (1990) reported on an association between bipolar disorder and a locus, contiguous to the insulin gene, containing the gene for tyrosine hydroxylase; and Del Zompo et al. (1990) reported on an association between bipolar and especially bipolar schizoaffective disorder and heterozygous thalassemia in Southern Sardinia. Because of the closeness of the area containing the gene for B-hemoglobin, responsible for heterozygous B-thalassemia, and the region containing the tyrosine hydroxylase genes, the findings of Del Zompo and associates are of great heuristic significance.

[34] It was suggested that a gene linked with HLA-haplotype, located on chromosome 6, is responsible for the genetic-transmission of "bipolar affective disease". It should be noted, however, that this was not supported by the results of Goldin, Clerget-Darpoux and Gershon (1982), and Suarez and Croughan (1982). The findings of the original reports could not be replicated and were also challenged on statistical grounds by Goldin and Gershon (1983).

study sample by bipolar disorders, other than manic-depressive disease, e.g., cycloid psychoses, unsystematic schizophrenias.

Dementia Praecox

The origin of Kraepelin's (1899) nosologic concept of dementia praecox was in the diagnostic concept of démence precoce, first described by Morel in 1852.[95] For Kraepelin, dementia praecox was an all embracing diagnostic concept which included all the disorders with "a course leading to psychic invalidity of varying severity" and with "an outcome arising from a peculiar destruction of the personality's inner integrity, whereby emotion and volition in particular are impaired."[96]

By replacing the term dementia praecox with the term schizophrenia and redefining schizophrenia as a "group of

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[95] MOREL'S first description of the disorder was in his ÉTUDE CLINIQUES, published in 1852-1853. However, it was only seven years later in 1860, in his TRAITÈ DES MALADIES MENTALES, that he introduced the term "démence precoce".

[96] Kraepelin's (1913) final formulation of "dementia praecox" was published in the eighth edition (1909-1915) of his textbook. Kraepelin's diagnostic criteria of "schizophrenic psychoses" in the monograph of Berner et al (1983) are based on this final formulation of the diagnostic concept. It was also in the eighth edition, that Kraepelin distinguished among ten different forms and the following nine different end-states of "dementia praecox": "cure", "cure with defect", "simple deterioration", "imbecility with confusion of speech", "hallucinatory deterioration", "hallucinatory insanity", "dementia paranoides", "flighty, silly deterioration" and "dull, apathetic dementia".

psychoses" characterized "by a specific type of thinking, feeling and relation to the external world" which "appears in no other disease in this particular fashion", Eugen Bleuler (1911) consolidated the diagnostic concept"[9]. His fundamental, or basic symptoms"[10] remained for well over 50 years the most extensively employed diagnostic criteria for schizophrenia, which, only in recent years has been replaced by Kurt Schneider's (1957) first

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[9] The term "schizophrenia" was introduced in the title of BLEULER'S monograph, DEMENTIA PRAECOX ODER DER GRUPPE DER SCHIZOPHRENIEN, published in 1911 by Deuticke in Leipzig. The monograph was reprinted in 1978 by Minerva Publications in Munich; and translated from the original German into English by J. ZINKIN. The English edition was published in 1950 under the title DEMENTIA PRAECOX OR THE GROUP OF SCHIZOPHRENIAS, by International University Press in New York.

[10] Bleuler (1911) considered the fundamental or basic symptoms of schizophrenia, such as loosening of associations, inappropriateness of affect, ambivalance and autism, exclusive for the disorder. In contradistinction to the basic symptoms, the accessory symptoms, such as delusions, hallucinations and catatonic symptoms, he believed, may occur in other psychiatric conditions as well. The basic symptoms, which assumedly display the fundamental disturbance of schizophrenia, are frequently referred to as the four A's. In addition to the basic and accessory symptoms, Bleuler also distingusihed between primary and secondary symptoms of schizophrenia. He assumed that the primary symptoms such as disturbance of associations, affective changes, hallucinations, stereotypes and physical disorders are the direct expressions of the brain disease, whereas the secondary symptoms are psychologically understandable reactions to the disease process.

rank symptoms"[99].

Results of "family-genetic" studies are in support of the contention that schizophrenia is a genetically meaningful[100] nosologic category. Morbidity risk to develop schizophrenia among the brothers and sisters of schizophrenics was found to be approximately ten times higher (8.5 %), and among the children of schizophrenics, approximately 15 times higher (12.3 %), than in the general population (0.86 %)[101] (Slater and Cowie, 1971).[102] Supportive also are the findings that the risk to develop

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[99] KURT SCHNEIDER'S "first rank symptoms" were first published in 1957, in his paper PRIMÄRE UND SECUNDÄRE SYMPTOME BEI SCHIZOPHRENIE. They include audible thoughts, the hearing of voices that comment on what one is doing at the time, somatic passivity experience, thought withdrawal, thought broadcasting, delusional perceptions, and feelings of alien influences. The detection of first rank symptoms represents a pragmatic approach to the diagnosis of schizophrenia. In spite of their extensive use, however, Mellor (1982) has shown that the presence of first rank symptoms are not exlusive for schizophrenia.

[100] Genetically meaningful in relationship to schizophrenia implies, that within the population included under schizophrenia there is at least one genetically distinctive nosologic category.

[101] The risk figure of 0.86 percent for schizophrenia in the general population, given by TSUANG and VANDERMEY (1980) in their monograph, GENES AND THE MIND, is based on a pool of 19 studies from six countries.
According to Fish "the expectation of schizophrenia for the European population is about 0.85 percent ranging from 0.42 percent in Germany to 1.25 percent in Sweden. In Switzerland it is 2.38 percent, but this higher rate is almost certainly due to the influence of Bleuler's concept of schizophrenia" (Hamilton, 1976).

[102] The figures relevant to the risk to develop schizophrenia among the relatives of schizophrenics, given in the monograph of SLATER and COWIE (1971) on THE GENETICS OF MENTAL DISORDER, are primarily based on the figures in the monograph, ENDOGENE PSYCHOSEN by ZERBIN-RUDIN (1967), published in the second volume of HUMAN GENETIK, EIN KURZES HANDBUCH, edited by P. BECKER (1967) (Tsuang and Vandermey, 1980).

schizophrenia among fraternal twins of the same sex is more than twice as high (12.0 %) than for fraternal twins of the opposite sex (5.6 %)[103] (Shields and Slater, 1967).[104] However, the strongest impetus in support of the contention that schizophrenia is a genetically meaningful nosologic category is, that, with the exception of the clinical study of Tienari (1963),[105] there is no overlap in concordance rates between monozygotic-identical twins and dizygotic-fraternal twins. Concordance rates are consistently higher in the former than in the latter.

While the risk for schizophrenia was found to be consistently higher among the relatives of schizophrenics than in the general

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[103] Same sex fraternal-twin pairs have similar sex chromosomes and therefore they are genetically more similar than opposite-sex fraternal-twin pairs. Hence, in a genetically transmitted disease, concordance rate for fraternal-twins of the same sex should be higher than for fraternal-twins of the opposite sex.

[104] The risk figures given by Tsuang and Vandermey (1980) for fraternal twins of the same sex and of the opposite sex (i.e., 12% and 5.6% respectively) are based on pooled data derived from the paper GENETIC ASPECTS OF SCHIZOPHRENIA by SHIELDS AND SLATER (1967).

[105] TIENARI'S (1963) monograph, PSYCHIATRIC ILLNESS IN IDENTICAL TWINS was published in Acta Psychiat. Scand. It is the only published report in which the concordance rate for schizophrenia in identical twins is lower than the concordance rate for fraternal twins in any of the other published reports, including Essen-Moller's (1941), Fischer, Harvald and Hauge (1969), Gottesman and Shields' (1966), Kringlen's (1966), and Rosanoff et al.'s (1934). But even in Tienari's study, within the study population, concordance rate was higher among monozygotic twins (6%), than among dizygotic twins (5%).

population (Altschuler, 1957)[106], and concordance rate of schizophrenia was found to be consistently greater in monozygotic than in dizygotic twins, there is a great variation in reported concordance rates of schizophrenia in identical twins. This is to the extent that concordance rate in monozygotic twins, identified by permissive criteria of schizophrenia, ranges from 27 (Allen, Cohen and Pollin, 1972) to 71 percent (Essen-Moller, 1941), and identified by strict criteria of schizophrenia, ranges from 6 (Tienari, 1963) to 50 percent (Luxenburger, 1928), with a pooled concordance rate of 45.6 percent (Tsuang and Vandermey, 1980).[107] These figures are not sufficiently high[108] to provide support for the contention that schizophrenia is a genetically valid

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[106] ALTSCHULER (1957), in his paper, GENETIC ELEMENTS IN SCHIZOPHRENIA, gave the following expectancy rates for schizophrenia: general population - 0.85%, half siblings - 7 to 8%, full siblings - 5 to 15%, parents - 5 to 10%, children of one index case - 8 to 16% and children of two index cases - 53 to 86%. Altschuler's figures were adopted by FISH (1962) in his monograph, SCHIZOPHRENIA, and by BAN (1973) in his monograph, RECENT ADVANCES IN THE BIOLOGY OF SCHIZOPHRENIA.

[107] The figures quoted regarding concordance rate for schizophrenia in identical twins diagnosed by permissive and strict criteria are based on the reports of Luxenburger (1928), Rosanoff et al. (1934), Essen-Moller (1941), Kallman (1946), Slater (1953), Inouye (1963), Tienari (1963), Kringlen (1966), Gottesman and Shields (1966), Fischer, Harvald and Hauge (1969) and Allen, Cohen and Pollin (1972). The figures from these publications are summarized in a table by Goodwin and Guze (1989)in their monograph, PSYCHIATRIC DIAGNOSIS. The pooled concordance rate quoted, is adopted from Tsuang and Vandermey (1980).

[108] While concordance rate in identical twins is not sufficiently high to support that schizophrenia is a genetically transmitted disease, Boklage (1977) in his study found, that concordance rate for schizophrenia in monozygotic twins was close to 100 percent when both twins were right handed, whereas it was considerably lower when that was not the case. On the basis of these findings he suggested "that the risk of schizophrenia is somehow associated with the process of brain lateralization". Findings in replication studies (Luchins, Pollin and Wyatt, 1980; Taylor et al., 1982), however, have remained inconsistent (Goodwin and Guze, 1989).

concept[109], and suggest, that what is diagnosed as schizophrenia, consists of two or more genetically distinctive disorders.[110]

Unsystematic Schizophrenias

Genetic research in schizophrenia led to a re-evaluation of the unitary nosologic concept[111] of dementia praecox. This, in turn,

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[109] Genetic heterogeneity implies "that what is usually lumped under one name -- 'schizophrenia' -- is actually an Irish stew of separate diseases, each type caused by its own specific gene or combination thereof and having its own distinct mode of transmission, but all disguised under one broth of clinical symptoms. Most researchers in psychiatric genetics now agree that schizophrenia is not a unitary disorder, although they by no means agree how it should be properly subdivided" (Tsuang and Vandermey, 1980)

[110] In keeping with the contention that schizophrenia consists of two or more nosologically distinctive diseases are the findings of Matthysse and Kidd (1976) that neither the single major locus model (Rosanoff and Orr, 1911; Rudin, 1916; Leonhard, 1934; Kallmann, 1938, 1946; Book, 1953; Slater, 1958; Elston and Campbell, 1970; Heston, 1970; and Slater and Cowie, 1971), nor the polygenic models with a large number of additive loci (Crittenden, 1961; Falconer, 1965, 1967; Karlsson, 1968; Reich et al., 1972, 1975) can account for the observed frequency of schizophrenia in first degree relatives of schizophrenic probands". In keeping also are the findings of Stewart, Debray and Caillard (1980), who, on the basis of the recognition that direct likelihood comparisons failed to distinguish the one -, two -, and four - locus models simulated, suggested, that the etiology of schizophrenia is either nongenetic or heterogeneous. (Information relevant to this topic is reviewed and discussed by O'ROURKE ET AL. in their paper, REFUTATION OF THE GENERAL SINGLE-LOCUS MODEL FOR THE ETIOLOGY OF SCHIZOPHRENIA, published in 1982.)

[111] The unitary nosologic concept of schizophrenia culminated in the work of CONRAD (1958), who perceived schizophrenia as one disease in which the loosening of the coherence of perception and thought results in the fragmentation of psychic activity with the emergence of new Gestalten. In his monograph, DIE BEGINNENDE SCHIZOPHRENIE Versuch einer Gestaltanalyse des Wahns, on the basis of the course of the illness, Conrad described five progressive stages and seven different types of schizophrenia. (Reviewed by FISH in his monograph, SCHIZOPHRENIA published in 1962 and 1976, and by BAN in his monograph on RECENT ADVANCES IN THE BIOLOGY OF SCHIZOPHRENIA, published in 1973).

"based on current knowledge about age and sex distributions, clinical symptoms, presence of triggering life-experiences, patterns of transmission within families, existence of genetic factors, and many other kinds of information" led Tsuang and Vandermey (1980) to separate within schizophrenia organic and true (i.e., sui generis) schizophrenic disorders; and within the true schizophrenic disorders, atypical and typical forms.[111]

The origin of Leonhard's (1936, 1957) diagnostic concepts of unsystematic and systematic schizophrenia, was in the diagnostic concepts of atypical and typical schizophrenias of KARL KLEIST (1923), presented in his paper DIE AUFFASSUNG DER SCHIZOPHRENIEN ALS SYSTEM KRANKHEITEN (Table X). Similar to Kleist, Leonhard maintained that these two distinctive categories of schizophrenic psychoses are unrelated to each other and are

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[111] One of the early dichotomies within schizophrenic disorders, is the distinction between schizophreniform and schizophrenic psychoses. It was put forward by LANGFELDT (1937, 1939) in his monographs THE PROGNOSIS IN SCHIZOPHRENIA AND THE FACTORS INFLUENCING THE COURSE OF THE DISEASE (1937) and, THE SCHIZOPHRENIFORM STATES (1939). In Langfeldt's classification schizophreniform psychosis, in contradistinction to schizophrenic psychosis, is characterized by good premorbid personality, presence of precipitating factor, acute onset, mixed clinical picture and favorable environmental conditions prior and after the outbreak of disease. Langfeldt's separation of schizophreniform psychosis or "good prognosis schizophrenia" from "bad prognosis schizophrenia", received substantial support in the work of Stephens and Astrup (1963) and Vaillant (1963).

One of the late dichotomies within schizophrenic disorders, is the distinction between "type I" and a "type II" syndromes. It was proposed by CROW (1980) in his paper, MOLECULAR PATHOLOGY OF SCHIZOPHRENIA: MORE THAN ONE DISEASE PROCESS? In Crow's dichotomy, the type I syndrome, in contradistinction to the type II syndrome, is characterized by positive symptoms, acute onset, favorable response to neuroleptics, absence of intellectual impairment, reversibility in terms of outcome and increase in dopamine receptors.

Table I

DIAGNOSTIC CATEGORIES	TYPICAL	ATYPICAL
Hebephrenias	Silly hebephrenia Depressive hebephrenia Apathetic hebephrenia Autistic hebephrenia	
Catatonias	Negativistic catatonia Proskinetic catatonia Akinetic catatonia Stereotyped catatonia Parakinetic catatonia Speech-inactive catatonia Speech-prompt catatonia	Iterative catatonia
Paranoias	Progressive somatopsychosis Progressive autopsychosis Progressive confabulosis Phantasiophrenia Progressive influence psychosis Progressive inspiration psychosis	
Paraphrenias		Circumscribed delusional psychosis Progressive signification psychosis Progressive self-reference psychosis
Confusiophrenias	Incoherent schizophrenia Paralogical schizophrenia Schizophasia	Shift-like confused schizophrenia

Kleist's (1923, 1943, 1957) classification of schizophrenias; 26 subtypes, belonging to five categories and two major classes (typical and atypical) of disorders. Based on Silveira's (1961) presentation at the Third World Congress of Psychiatry.

grouped together only by "custom." The category of systematic schizophrenias is comprised of a group of disorders, characterized by the purity (in terms of diagnoses) of psychopathology, and the constancy (i.e., simple-monomorphous nature) of the clinical picture, as well as by a continuous and progressive course; whereas the category of unsystematic schizophrenias is comprised of a group of disorders, characterized by the multiplicity of psychopathology and the rapid changes (i.e., multiform-polymorphous nature) of the clinical picture, as well as by an episodic and partially remitting course.[111]

Supportive of the distinctiveness of unsystematic and systematic schizophrenias, are the results of family-genetic studies, which indicate, that morbidity risk for endogenous psychoses is considerably higher in the relatives of patients with unsystematic schizophrenia than in the relatives of patients with systematic

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[111] In his Introduction to Part III of his monograph, THE CLASSIFICATION OF ENDOGENOUS PSYCHOSES, LEONHARD (1978) wrote: "Systematic and unsystematic schizophrenias have essentially nothing to do with each other. The common name is justifiable only in terms of tradition because, since Kraepelin and Bleuler, all endogenous psychoses leading to defects have been grouped as schizophrenias. The deep parallels of the unsystematic schizophrenias are much closer to the cycloid psychoses than to the systematic schizophrenias.....The differential diagnosis is often difficult. On the other hand, one rarely has any trouble differentiating between a systematic and an unsystematic schizophrenia. Not only are the symptomatic pictures completely different, but the courses as well are fully different. The systematic forms display a creeping progressive course, while the unsystematic forms may go into remission or may even be clearly periodic. A periodic catatonia can produce as many attacks as a manic-depressive disease. Bipolarity is also characteristic for the unsystematic schizophrenias."

schizophrenia. In Leonhard's (1936) original Frankfurt sample of 530 cases, consisting of 440 patients with systematic schizophrenia and 90 patients with unsystematic schizophrenia, it was found, that only 5 percent of the patients with systematic schizophrenia had relatives hospitalized with endogenous psychoses, whereas 37 percent of the patients with unsystematic schizophrenia had relatives hospitalized with such diagnoses.[114] Corresponding figures in Leonhard's (1979) Berlin sample,[115] were 17.5 percent and 70.2 percent;[116] and in Astrup, Fossum and Holmboe's (1962) Oslo sample, were 14 percent and 36 percent respectively.[117]

Interpretation of findings in family-genetic studies of

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[114] In another study, based on Leonhard's Frankfurt sample, Schulz and Leonhard (1940) found that morbidity risk for schizophrenia, is only slightly higher among the relatives of patients with unsystematic schizophrenia, than among the relatives of patients with systematic schizophrenia.

[115] Information on the Berlin sample was first reported by TROSTORFF (1975) in her paper VERLAUF UND PSYCHOSE IN DER VERWANDTSCHAFT BEI DEN SYSTEMATISCHEN UND UNSYSTEMATISCHEN SCHIZOPHRENIEN UND DEN ZYKLOIDEN PSYCHOSEN. There are some minor differences between the data presented by Trostorff and the data presented by Leonhard, because "....some cases which she counted as combined-systematic now appear to have been simple systematic. Furthermore, a sick sister was added to the count of sick siblings of one patient with periodic catatonia" (Leonhard, 1979).

[116] In his Berlin sample, Leonhard (1979) found an 11.6 percent morbidity risk for parents of patients with unsystematic schizophrenia, and a 2.2 percent morbidity risk for parents of patients with systematic schizophrenia.

[117] In their Norwegian sample, Astrup, Holmboe and Fossum (1962) found that the difference between the percentage of patients with unsystematic schizophrenia, whose relatives suffer from unsystematic schizophrenia, and the precentage of patients with systematic schizophrenia, whose relatives suffer from systematic schizophrenia, was not impressive (i.e., 52% and 48% respectively).

schizophrenia must be made with extreme caution, because the difference in disease rate among the siblings of patients with unsystematic (11-12%) and systematic schizophrenias (2-3%), can easily be covered up by faulty sampling,[118] e.g., by the inclusion of patients with cycloid psychoses (with a disease rate of 4.7% in the siblings) among the unsystematic schizophrenias.[119]

Cycloid Psychoses

The origin of Leonhard's (1957, 1961, 1967) diagnostic concept

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[118] Leonhard (1979) firmly believed that there is a genetic difference between the unsystematic and the systematic schizophrenias. Mitsuda, similar to Leonhard, in his monograph, Clinical Genetics in Psychiatry, published in 1967, reported on a genetic difference between the atypical and typical schizophrenias.

[119] Leonhard (1979) focused attention on the great number of psychoses in the families of patients with periodic catatonia (65 related cases from 64 probands); the great number of diseased relatives of patients with cataphasia (71.2%); the relatively great number of affected siblings (10.7%) with the relatively small number of affected parents in affect-laden paraphrenia; and the relatively high incidence of affected relatives in parakinetic catatonia in comparison to other systematic schizophrenias in general and systematic catatonias in particular.

of cycloid psychosis[130] is in the diagnostic concepts of autochthonous degeneration psychosis and cycloid marginal psychosis of KARL KLEIST (1921, 1928), presented in his papers, AUTOCHTHONE DEGENERATION PSYCHOSEN and ÜBER ZYKLOIDE, PARANOIDE UND EPILEPTOIDE PSYCHOSEN UND ÜBER DIE FRAGE DER DEGENERATION

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[130] The origin of the diagnostic concept of cycloid psychosis was in the work of Legrain (1886) and Magnan (1893), who recognized that within Morel's (1860) degeneration psychoses (i.e., psychoses which are the result of a degenerative process within a given family) there were illnesses with an acute or subacute onset (Legrain, 1886), which followed a phasic, episodic course (Magnan, 1893) with full remissions between episodes. The concept was further elaborated by Schroder (1926) who referred to this group of disorders as metabolic psychoses in order to highlight their episodic nature. Gaupp (1926) called them mixed (combinierte) psychoses, because of the mixture of schizophrenic cross-sectional psychopathology with a longitudinal course resembling manic-depressive illness. The separation of two distinctive illnesses from this mixed group of psychoses, i.e., motility psychosis (Wernicke, 1899) and confusion psychosis (Kleist, 1928), yielded the concepts of autochthonous degeneration psychosis and cycloid marginal psychosis (which included both, motility and confusion psychoses) in the work of Kleist (1921, 1928). Subsequently, the identification of a third distinctive illness, anxiety-happiness psychosis (Leonhard, 1934), resulted in the present concept of cycloid psychosis, which includes confusion, anxiety-happiness and motility psychoses (Leonhard, 1957). (The historical development of cycloid psychosis was reviewed by FISH in his paper THE CYCLOID PSYCHOSES, published in 1964 (a), and by BROCKINGTON, PERRIS and MELTZER in their paper, CYCLOID PSYCHOSES: Diagnosis and Heuristic Value, published in 1982.)

PSYCHOSEN[121] (Table XI). They refer to a category of mental disorders with a cross-sectional psychopathology similar to that seen in the unsystematic schizophrenias,[122] and a longitudinal-course of illness similar to that seen in the phasic psychoses, e.g., manic depressive disease.[123]

The nosologic concept of cycloid psychosis was further elaborated by PERRIS (1973, 1974), who in his paper, CYCLOID PSYCHOSES: HISTORICAL BACKGROUND AND NOSOLOGY, and monograph, STUDY OF CYCLOID PSYCHOSIS, shifted the

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[121] Many of the diagnostic concepts presented by Kleist (1921, 1928) were first described by Wernicke (1900), e.g., anxiety psychosis, expansive autopsychosis with autochthonous ideas, psychic motility psychosis, periodic maniacal autopsychosis or agitated confusion and intrapsychic akinesia. Sometimes Kleist used a different term than Wernicke for the same diagnostic concept. For example he referred to Wernicke's inhibited confusion psychosis as confused stupor.

[122] The three forms of cycloid psychosis correspond with the three forms of unsystematic schizophrenia, i.e., confusion psychosis corresponds with cataphasia, anxiety-happiness psychosis with affect-laden paraphrenia and motility psychosis with periodic catatonia. Because of their great similarities, Wernicke (1900) did not consider periodic catatonia as a clearly distinctive diagnosis from motility psychosis. It was only in FUNFGELD's (1936) monograph, DIE MOTILITATPSYCHOSEN UND VERWIRRTHEITEN, published by Karger in Berlin, that these two disorders were clearly separated.

[123] LEONHARD in his lecture at the Royal Edinburgh Hospital for Nervous and Mental Disorders on the 27th of June in 1960, defined cycloid psychosis as a group of acute, reversible psychoses which do not fulfill the criteria of schizophrenic or manic-depressive illness. He emphasized that in contradistinction to the unsystematic schizophrenias, there is no overlap between the two poles in any one of the three cycloid psychoses. He also emphasized that the three cycloid psychoses are not sharply separated from each other. The presentation was published in 1961 under the title CYCLOID PSYCHOSES - ENDOGENOUS PSYCHOSES WHICH ARE NEITHER SCHIZOPHRENIC NOR MANIC DEPRESSIVE, in the Journal of Mental Science.

Table II

PATHOGENESIS COURSE	PHASIC COURSE		SHIFT-LIKE
	Simple-Monopolar Pattern	Multiform-Bipolar Pattern	
Affective	Hypochondriacal agitation	Acute anxious-ecstatic hallucinosis	Episodic hypnotic states
	Hypochondriacal depression		
	Anxious reference psychosis		
	Perplexed strangeness psychosis		
Constive	Expansive confabulations	Mimetic-hyperkinetic motility psychosis	Periodic morbid impulses
Intellectual	Ecstatic inspiration psychosis	Stuporous-agitated confusion	Episodic twilight states
		Acute perplexed interpretation psychosis	

Kleist's (1921) classification of "autochthonous degeneration psychoses." Based on Silveira's (1961) presentation at the Third World Congress of Psychiatry.

emphasis in the diagnosis of cycloid psychosis, from paranoid anxiety and/or motility extremes, to acute onset and polymorphic (multiform) symptomatology with confusion.[124]

In support of the distinctiveness of cycloid psychoses from the schizophrenic psychoses are findings in the family-genetic studies of Trostorff (1968) and Ungvari (1985), which indicate, that the morbidity risk for endogenous psychoses is consistently lower (5 % and 3.7 % according to the two authors respectively) in the parents of patients with cycloid psychosis, than in the parents of patients with unsystematic schizophrenia (11.6 % and 11.5 % respectively), and consistently higher than in the parents of patients with systematic schizophrenia (1.5 % and 1.3 % respectively). Furthermore, findings with multiple threshold analyses, carried out in Ungvari's sample, indicate that the cycloid psychoses are genetically distinctive from the systematic

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[124] Perris (1974) defined cycloid psychosis in terms of symptomatology, severity, and course. According to him, in terms of symptomatology, cycloid psychosis is characterized by mood swings and two or more of the following manifestations: (a) various degrees of confusion (from slight perplexity to gross disorientation) with agitation or retardation, (b) paranoid-like symptoms (delusions of reference, or influence, or persecution, etc.) and/or hallucinations not syntonic (congruent) with the mood state, (c) motility disturbances (hypo-or hyperkinesia), (d) occasional episodes of states of ecstasy, and/or (e) pananxiety. In terms of severity it is characterized by psychotic or occasionally psychotic manifestations (with regard to globality and disturbed reality evaluations) during the course of an episode. In terms of course it is characterized by single episode or recurrent episodes with periods of complete remission between without defect and without sensitiveness to changes in environment (e.g. hospital admission). Of particular importance in the diagnostic process is the polymorphic clinical picture with all sorts of symptoms "jumbled", suggesting the presence of several different disorders, none of which is dominant or persistent.

schizophrenias.[125]

In support also of the distinctiveness of cycloid psychosis and manic-depressive disease are Leonhard's (1979) findings (in his Berlin sample), that morbidity risk for endogenous psychosis is consistently higher (9.5 % and 10.6 % respectiveley) in the parents and siblings of probands with manic-depressive disease, than in the parents and siblings of probands with cycloid psychosis (4.6 % and 4.7% respectively).[126]

However, the strongest support in favor of the contention that cycloid psychosis is a genetically meaningful[127] nosologic category, was given by the findings of the high "nosologic homotypy" for cycloid psychosis. Accordingly, in Ungvari's (1985) sample, 57 percent, and in Perris' (1974) sample, 77 percent, of the parents and siblings of patients with cycloid psychosis, who were affected

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[125] In Ungvari's (1985) study multiple threshold analysis yielded genetic distinctiveness between the cycloid psychoses and the systematic schizophrenias, but not between the cycloid psychoses and the unsystematic schizophrenia. However, phenotypic correlations were strongly in favor of the contention that the category of unsystematic schizophrenias represent the link between the cycloid psychoses and the systematic schizophrenias.

[126] It was noted that in Leonhard's (1979) Berlin sample morbidity risk for endogenous psychosis among the parents of patients with anxiety-happiness psychosis was 6.7 percent, i.e., closer to manic-depressive disease (9.5 %), than to the other two cycloid psychoses, i.e., confusion psychosis (3.2 %) and motility psychosis (2.2 %).

[127] Genetically meaningful in relationship to cycloid psychosis implies that within the population included under cycloid psychosis there is at least one nosologically distinctive category.

by an endogenous psychosis, suffered from cycloid psychoses[128].

Phasic Psychoses

The term, phasic psychoses, was first used by EDDA NEELE in the monograph, DIE PHASISCHEN PSYCHOSEN, published in 1949. The term was adopted by Leonhard (1957), who employed it in reference to a category of episodic affective disorders with full remissions between episodes.[129]

With consideration to the contributions of Lange (1897) and Schou (1927), Leonhard (1957) divided phasic psychoses into two major categories, i.e., a bipolar or polymorphous (multiform), with a potential to be displayed in different episodes by psychopathologic symptoms in the opposite direction (i.e., elation and depression), and a unipolar or monomorphous (simple) disorder, with no such potential, displayed in different episodes by psychopathologic symptoms in the same direction (i.e., elation or depression).

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[128] The contention that cycloid psychosis is a nosologically distinctive category within the endogenous psychoses was supported also by the results of CUTTING, CLARE and MANN (1978), presented in their paper CYCLOID PSYCHOSIS: AN INVESTIGATION OF THE DIAGNOSTIC CONCEPT. In a follow-up examination of 90 percent of their 73 patients with cycloid psychosis these authors found, that compared with other psychoses, patients with cycloid psychosis had the highest recovery rate from the index episode (90 %), the highest proportion of subjects with at least one remission and the highest admission and episode rates (0.28 or 0.30/year respectively). They spend more time in hospital than depressed and manic patients (0.86 month/year, compared to 0.24 and 0.46 month/year respectively), but much less time than schizophrenic patients (2.52 month/year).

[129] Leonhard's (1957) early work, relevant to the phasic psychoses, was based on cases admitted to the Frankfurt Nerve Clinic in the years from 1938 to 1942. Leonhard's original sample of phasic psychoses consisted of 526 patients. In Berlin, his sample of phasic psychoses increased to 1163 (including the 167 patients with manic-depressive disease).

Furthermore, with consideration to Kleist's (1943, 1947) contributions[130], Leonhard separated within the unipolar phasic psychoses, "complete" (i.e., pure melancholia and pure mania) and "incomplete" (i.e., pure depressions and pure euphorias) forms.

Results of early family-genetic studies are in support of the contention, that the bipolar-unipolar dichotomy is a genetically meaningful distinction[131] within the affective disorders (Angst, 1966; Perris, 1966; Winokur and Clayton, 1967).[132] In his Berlin sample, Leonhard (1979) found that the frequency of endogenous psychoses in both, the siblings and the parents of patients with

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[130] In the first paragraph of his chapter on "Manic Depressive Disease", Leonhard (1979) wrote: "Until very recently nearly all psychiatrists were united in the opinion that the manic and the depressive disease pictures were all part of the manic-depressive disease.....Previously, Kleist had claimed that there was no independent manic-depressive disease, but rather only a melancholy and a mania with a certain reciprocal affinity. Thus he had already claimed the independence of the unipolar forms, but had gone too far by totally denying the independent existence of manic-depressive disease".

[131] Genetically meaningful in relationship to the unipolar and bipolar distinction implies that within the affective disorders there are at least two nosologically distinctive categories.

[132] In the first paragraph of the "Statistical Section" in his monograph, Leonhard (1979) wrote: "...Angst, and, independently, Perris and later Winokur et al. have published extensive statistics on unipolar and bipolar phasic psychoses confirming the different natures of these diseases. These authors have like myself, found that both the number and the length of the phases as well as the frequency among relatives are different although they did not base their proofs on these differences. Perris demonstrated that, in the relatives of unipolar patients, primarily unipolar forms reappear, and that the relatives of bipolar patients suffered primarily from bipolar forms. Angst examined sex distribution among psychoses in the relatives and found significant differences. Women dominated the sick relatives of the unipolar group. Frau v. Trostorff confirmed Angst's results, although she did not find the differences to be as great".

bipolar manic depressive disease was considerably higher (10.6 % and 9.5 % respectively) than in the siblings and parents of pooled unipolar disorders, i. e., pure melancholy pooled with pure mania (6.3 % and 6.4 % respectively), and pure depressions pooled with pure euphorias (3.9 % and 4.6 % respectively). He also found that while the number of phases was greater in bipolar (4.2) than in unipolar disorders[133], the mean length of the phases was shorter (5.5 month) in bipolar than in unipolar disorders.[134] In keeping with Leonhard's findings are reports in which bipolar and unipolar (affective) disorders were successfully separated (1) on the basis of heredity (Angst and Perris, 1968; Trostorff, 1968; Winokur, Clayton and Reich, 1969) with patients suffering from bipolar (affective) disorder having a higher incidence of familial affective illness (Perris, 1974) and mania (Winokur, 1973, 1979), than patients with unipolar disorders; and (2) on the basis of biologic factors, such as Type B monoamine oxidase (MAO) activity in the platelet[135] and 3-methoxy-4-hydrexyphenylglycol (MHPG)

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[133] The number of phases in Leonhard's (1979) Berlin sample was 2.4 in the pooled depressive population of unipolar disorders, i.e., pure melancholy and pure depressions; and 2.9 in the pooled manic population of unipolar disorders, i.e., pure mania and pure euphorias.

[134] The mean length of phases in Leonhard's (1979) Berlin sample was 3.6 months in the pooled unipolar populations of pure mania and pure euphorias; 8.1 months in the unipolar population of pure melancholy; and 11.2 months in the pooled unipolar populations of pure depressions.

[135] Murphy and Weiss (1972) found the activity of Type B monoamine oxidase in the platelet significantly lower in bipolar than in unipolar affective disorders.

concentrations in the urine.[136]

While findings in twin pairs, concordant for mood disorder, showed that 81 percent of the pairs were also concordant for polarity, other family-genetic study data on patients with bipolar--affective--disorder showed, that the increase in the incidence of affective disorders was not restricted to bipolar, but included also unipolar--affective--disorders (Tsuang and Vandermey, 1980)[137]. The same as to family-genetic data applies also to neuroendocrine measures, such as the serum cortisol changes to the administration of dexamethasone, and the thyroid-stimulating hormone response to the administration of the thyrotropin-releasing hormone (Amsterdam et al., 1982; Carroll, 1983; Schlesser, Winokur and Sherman, 1980; Spitzer, Endicott and Robins, 1978; Stokes et al., 1984; Targrum, 1983; Van Praag, 1982; and Zisook et al., 1985).[138] Because of

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[136] Goodwin and Post (1977) found a significantly lower (excretion) concentration of MHPG, the central metabolite of norepinephrine, in the urine of patients with bipolar than in unipolar affective disorders.

[137] The origin of the information in Tsuang and Vandermey's (1980) review, on the high concordance rate for polarity in twin pairs, concordant for mood disorder, is in the findings of Zerbin-Rudin (1967). The same findings were also referred to by PERRIS in his chapter on THE GENETICS OF AFFECTIVE DISORDER, published in 1974 in the volume, BIOLOGICAL PSYCHIATRY, edited by J. MENDELS. The origin of the information on the inconsistent family-genetic findings is in the papers of Angst (1966), Helzer and Winokur (1974), Goetzl et al (1974), Gershon et al. (1976) and James and Chapman (1976).

[138] A detailed review of findings in a series of validation studies regarding the unipolar-bipolar distinction was presented by AKISKAL (1983) in his chapter on THE BIPOLAR SPECTRUM: NEW CONCEPTS IN CLASSIFICATION AND DIAGNOSIS, published in PSYCHIATRY UPDATE: THE AMERICAN PSYCHIATRIC ASSOCIATION ANNUAL REVIEW, edited by L. GRINSPOON. Prior reviews of the same topic were published by Goodwin and Bunney (1973), Akiskal and McKinney (1975), Depue and Monroe (1978), Gershon (1978) and Dunner (1980).

this, in spite of all supporting data, the controversy, regarding the distinctiveness of unipolar and bipolar affective disorders cannot be considered as resolved.[139]

Current Classifications

ICD-9

The structurally determined psychoses reviewed, are included under the categories of schizophrenic and affective psychoses, i.e., the two major groups of other psychoses, in the ICD-9.

The ICD-9 concept of schizophrenic psychoses is based on Bleuler's (1911) syndromic definition, with consideration to Schneider's (1957) first rank symptoms.[140] As such, it is an all embracing diagnostic concept, which includes both, the systematic and the unsystematic forms of schizophrenia, as well as the cycloid

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[139] Gershon, et al. (1976) contended that, if there is an underlying genetic division in mood disorders, this division does not correspond well with the unipolar-bipolar distinction. Similar conclusions were reached by Smeraldi, Negri and Melica (1977) and by Taylor and Abrams (1980). On the other hand, Tsuang and Vandermey (1980) maintained that genetically, unipolar and bipolar disorders are two separate illnesses.

[140] In the ICD-9, schizophrenic psychoses are defined as "a group of psychoses in which there is a fundamental disturbance of personality, a characteristic distortion of thinking, often a sense of being controlled by alien forces, delusions which may be bizarre, disturbed perception, abnormal affect out of keeping with the real situation, and autism. Nevertheless, clear consciousness and intellectual capacity are usually maintained.....The diagnosis 'schizophrenia' should not be made unless there is, or has been present during the same illness, characteristic disturbance of thought, perception, mood, conduct, or personality--preferably at least in two of these areas. The diagnosis should not be restricted to conditions running a protracted, deteriorating, or chaotic course....."

psychoses[141] (Leonhard, 1957). Accordingly, it extends beyond the hebephrenic, catatonic and paranoid types, of Kraepelin's dementia praecox (1899) to include simple schizophrenia, described by Diem (1903),[142] latent schizophrenia described by Bleuler (1911),[143]

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[141] Cycloid psychoses (Leonhard, 1957) are included in the ICD-9, as schizoaffective type of schizophrenic psychoses (also referred to as cyclic schizophrenia, mixed schizophrenic and affective psychosis and schizophreniform psychosis, affective type). The disorder is defined as "a psychosis in which pronounced manic and depressive features are intermingled with schizophrenic features and which tends towards remission without permanent defect, but which is prone to recur".

[142] DIEM in his paper, DIE EINFACHE DEMENTE FORM DER DEMENTIA PRAECOX described a "simple form" of "dementia praecox". The paper was published in 1903 in Arch. Psychiat. Nervenkr. Eight years later Bleuler (1911) used the term "simple schizophrenia" to designate the "form" of "schizophrenia" with "marked formal thought disorder" and "flattening of affect" in the absence of "delusions", "hallucinations" and/or "catatonic symptoms". He adopted the term, "simple", from Pick, who, in 1891 "described a 'simplex' syndrome, which remained after the two groups described by Hecker (1871) and Kahlbaum (1874) had been separated from the broad category of Morel (1853)" (Fish, 1962). Recently BLACK and BOFFELI (1989), in their paper, SIMPLE SCHIZOPHRENIA: PAST, PRESENT AND FUTURE, gave a historical overview of the concept.

[143] The term, latent schizophrenia, was first used by BLEULER (1911) in his monograph, DEMENTIA PRAECOX ODER GRUPPE DER SCHIZOPHRENIEN, to designate "a group of psychoses with odd, distorted personalities, which he believed, were due to a schizophrenic process which had not been acute and had ceased to be active". In his monograph on Schizophrenia, Fish (1962) noted, that the concept of latent schizophrenia is not very helpful and is "beyond proof or disproof" (Hamilton, 1976). The term is included in the ICD-9 but "it is not recommended for general use". Included under the heading of "latent schizophrenia" are also "some other poorly defined varieties of schizophrenia", such as "borderline", "prepsychoptic" or "prodromal schizophrenia", and "pseudoneurotic" or "pseudopsychopathic schizophrenia".

schizoaffective psychosis, described by Kasanin (1933),[144] acute schizophrenic episode,[145] and residual schizophrenia.[146]

In variance with the ICD-9 concept of schizophrenic psychoses, which is based on Bleuler's (1911) definition, the ICD-9 concept of affective psychoses is based on Kraepelin's (1896) original definition of manic-depressive insanity.[147] As such, it embraces both, the bipolar and the unipolar phasic psychoses, including the

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[144] KASANIN, in his paper THE ACUTE SCHIZOAFFEECTIVE PSYCHOSES, published in 1933, described a group of patients with concurrent schizophrenic and affective symptoms. In spite of the fact that these patients recovered from their symptoms, Kasanin diagnosed them as having a subtype of schizophrenia (Kaplan and Sadock, 1988). Prior to Kasanin, similar cases were described by Kirby (1913) and Hoch (1921), but classified as manic-depressive psychosis.

[145] THE ICD-9 concept of acute schizophrenic episode corresponds with the diagnostic concept of oneirophrenia described by MEDUNA and McCULLOCH (1945) in their paper THE MODERN CONCEPT OF SCHIZOPHRENIA. Prior to them, MAYER-GROSS (1924) in his monograph, SELBSTSCHILDERUNG DER VERWIRRTHEIT: Das Oneroide Erlebnis, described the "oneroid experience". In the ICD-9, acute schizophrenic episode is characterized by a dream-like state with slight clouding of consciousness and perplexity. It is based on MEDUNA'S (1950) description in his monograph, ONEIROPHRENIA, published by Illinois University Press.

[146] In the ICD-9, residual schizophrenia is defined as "a chronic form of schizophrenia in which the symptoms that persist from the acute phase have mostly lost their sharpness. Emotional response is blunted and thought disorder, even when gross, does not prevent the accomplishment of routine work." Chronic undifferentiated schizophrenia is synonymous for residual schizophrenia in the ICD-9.

[147] The ICD-9 definition of manic-depressive psychosis corresponds with Kraepelin's original definition of manic-depressive insanity. It differs from his last (1921) definition which also includes the "slightest colorings of mood.....which on the one hand are to be regarded as the rudiment of more severe disorders, on the other hand, pass without sharp boundary into the domain of personal predisposition" (Akiskal, 1983).

manic, the depressive and the circular forms[148] (Table XII).

DSM-III

The structurally determined psychoses reviewed, are included under schizophrenic and affective disorders in the DSM-III. They represent two of the 15 categories of Axis I diagnoses.

Similar to the ICD-9 diagnostic concept of schizophrenic psychosis, the DSM-III diagnostic concept of schizophrenic disorders is based on the presence of characteristic symptoms (Schneider, 1957), involving multiple psychological processes (Bleuler, 1911) and deterioration from a previous level of functioning (Kraepelin, 1899). However, unlike in the ICD-9, in the DSM-III, the diagnosis of schizophrenia cannot be made without

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[148] In the ICD-9 affective psychoses are defined as "mental disorders usually recurrent, in which there is a severe disturbance of mood (mostly compounded of depression and anxiety, but also manifested as elation and excitement) which is accompanied by one or more of the following: delusions, perplexity, disturbed attitude of self, disorders of perception and behavior; these are all in keeping with the patient's prevailing mood (as are hallucinations when they occur".)

Table III

SCHIZOPHRENIC PSYCHOSES
- Simple type
- Hebephrenic type
- Catatonic type
- Paranoid type
- Acute schizophrenic episode
- Latent schizophrenia
- Residual schizophrenia
- Schizoaffective type
- Other
- Unspecified

AFFECTIVE PSYCHOSES

Manic-depressive psychosis,	Manic type
	Depressed type
	Circular type but currently manic
	Circular type but currently depressed
	Circular type, mixed
	Other and unspecified
	Other
	Unspecified

Classification of schizophrenic and affective psychoses in the ICD-9.

the presence of psychotic symptoms[189] during the active phase of the illness, in case of onset of symptoms after 45, and before the duration of symptoms of at least six months.[190] As a result, diagnoses, such as simple, latent and schizoaffective types[191] of

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[189] In contradistinction to the ICD-9, in the DSM-III, schizophrenic psychoses are referred to as schizophrenic disorders. Nevertheless, it is in the DSM-III, that psychotic symptoms are one of the essential prerequisites for the diagnosis of schizophrenia.

Because of the absence of psychotic symptoms both simple and latent schizophrenia are omitted from the DSM-III. They are perceived as personality disorders and included among the Axis II diagnoses of schizoid, schizotypal and borderline. This might need to be reconsidered in view of TORGERSEN'S (1984, 1985) findings of a "familial and even genetic relationship between schizophrenia and schizotypal personality", reported in his papers, GENETIC AND NOSOLOGICAL ASPECTS OF SCHIZOTYPAL AND BORDERLINE PERSONALITY DISORDERS and RELATIONSHIP OF SCHIZOTYPAL PERSONALITY DISORDER TO SCHIZOPHRENIA: GENETICS, published in Arch. Gen. Psychiat. and Schizophr. Bull., respectively. Similar findings were reported by Kendler, Gruenberg and Tsuang (1985) and Kendler, Masterson and Davis (1985). According to Goodwin and Guze (1989), the finding that there is a "familial and even genetic relationship between schizophrenia and schizotypal personality" is in support of "the validity of the schizophrenia-spectrum concept".

[190] Because the diagnosis of schizophrenic disorder cannot be used prior to the duration of at least six months of the manifestations, patients who otherwise fulfill criteria for schizophrenic disorder are diagnosed in the DSM-III as schizophreniform disorder, adopting the term, but not the concept of schizophreniform from Langfeldt (1939). However, the DSM-III concept of schizophreniform disorder does not correspond with the ICD-9 concept of acute schizophrenic episode, because it is not based on the presence of oneroid features.

[191] In the DSM-III, the diagnosis of schizoaffective disorder is included under the Axis I category of psychotic disorders not elsewhere classified. It does not correspond with the ICD-9 concept of schizoaffective type of schizophrenic psychosis. In the DSM-III, the category of schizoaffective disorder is retained "without diagnostic criteria for those instances in which the clinician is unable to make a differential diagnosis with any degree of certainty between 'affective disorder' and either 'schizophreniform disorder' or 'schizophrenia'", whereas, "some of the cases that in the past were diagnosed as 'schizoaffective disorder' are diagnosed as 'schizophreniform disorder', 'manic depression' or 'bipolar disorder' with 'mood congruent' or 'mood incongruent' features, or 'schizophrenia' with a superimposed 'atypical affective disorder'."

schizophrenia, as well as acute schizophrenic episode, are dismissed; and the different types of the disorder are restricted to the disorganized,[192] catatonic, paranoid, undifferentiated and the residual.[193]

The DSM-III diagnostic concept of affective disorders was formulated with consideration of Leonhard's (1957) contributions relevant to the dichotomy of bipolar and unipolar phasic (affective) psychoses. However, by shifting emphasis from the formal characteristics of polarity, expressed in the distinction between multiform-polymorph and simple-monomorph disease pictures, to the content of the manifest syndrome, expressed in the distinction between elation and depression, affective disorders in the DSM-III, are separated into bipolar disorders and depressions.[194] Furthermore, by replacing phenomenology with

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[192] The term hebephrenia (Hecker, 1871), was replaced in the DSM-III by the term, disorganized, and the disorder, which had been referred to in the ICD-9 as schizophrenic psychosis, hebephrenic type, is referred to in the DSM-III as schizophrenic disorder, disorganized type. The new name reflects a shift in emphasis in the diagnsotic concept from affective deterioration to incoherence of thinking with a considerable restriction of the population who fits diagnostic criteria. It should be noted that Bleuler (1911) considered hebephrenia as a "big kettle into which all forms that cannot be grouped into the other three headings" are thrown (Leonhard, 1978).

[193] While in the ICD-9, the diagnosis chronic undifferentiated schizophrenia is used as a synonym for the diagnosis of residual schizophrenia, in the DSM-III, the undifferentiated type differs from the residual type by the presence of prominent delusions, hallucinations, incoherence, or grossly disorganized thinking.

[194] The DSM-III restricts unipolar disorders to depressions. Because it does not recognise unipolar mania or unipolar euphorias, disorders, which are displayed by recurrent episodes of mania and/or hypomania, are included in the DSM-III under bipolar disorder, manic.

severity and duration as the primary organizing principle, affective disorders in the DSM-III, are subdivided into major (severe with short duration),[195] other specific (mild with prolonged duration),[196] and atypical[197] (Table XIII).

DSM-III-R

There is little difference between the DSM-III-R and the DSM-III in terms of the disorders discussed. However, the DSM-III term, schizophrenic disorder was replaced in the DSM-III-R, by the term, schizophrenia,[198] the term, affective disorder by the term, mood disorder, and the trichotomy within the affective disorders, by the dichotomy of bipolar disorders[199] and depressive

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[195] The DSM-III diagnostic concepts included under major affective disorders correspond to Leonhard's (1957) diagnostic concepts of manic-depressive disease, pure mania and pure melancholy, i.e., disorders with acute or subacute onset and relatively short duration.

[196] Of the two diagnoses included under other specific affective disorders in the DSM-III, one, i.e., dysthymic disorders, corresponds with the traditional diagnostic concept of depressive neurosis, whereas the other, i.e., cyclothymic disorder, does not correspond with traditional diagnostic concepts. The term was adopted from Schneider (1959) who used it as a synonym for manic-depressive disorder. The use of the term, however is more in keeping with Kretschmer's (1921) concept of cyclothymic temperament.

[197] The term atypical affective disorders refers to a residual category of affective disorders in the DSM-III. The same term was used by Ban (1989) to designate affective disorder with an insidious onset.
The term atypical depression refers to a residual category of depression in the DSM-III. The same term was used by Sargant (1961) to designate depression with hypersomnia and weight gain.

[198] Estimated prevalence rate for schizophrenia is from 0.2 percent to almost 1 percent.

[199] Estimated prevalence rate for bipolar disorder is from 0.4 percent to 1.2 percent.

Table XIII

SCHIZOPHRENIC DISORDERS
- Disorganized type
- Catatonic type
- Paranoid type
- Undifferentiated type
- Residual type

AFFECTIVE DISORDERS
- Major affective disorders
  - Bipolar disorder
    - mixed
    - manic
    - depressed
  - Major depression
    - single episode
    - recurrent
- Other specific affective disorders
  - Cyclothymic disorder
  - Dysthymic disorder
- Atypical affective disorders
  - Atypical bipolar disorder
  - Atypical depression

Classification of schizophrenic and affective disorders in the DSM-III.

disorders[160] (Table XIV).

ICD-10

Disorders relevant to the structurally determined psychoses reviewed, are included under two disease categories in the ICD-10, i.e., (1) schizophrenia, schizotypal[161] and delusional disorders and (2) mood (affective) disorders. The ICD-9 concept of schizophrenia includes the controversial diagnostic concept of post-schizophrenic depression,[162] among the seven subforms of

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[160] Estimated prevalence rate for major depression is from 9 precent to 26 percent in females and from 5 percent to 12 percent in males.

[161] Schizotypal disorder is perceived in the DSM-III-R as a personality disorder, and as such, it is an Axis II diagnosis. In the ICD-10 , it is perceived as a disease, similar to schizophrenia, but without psychotic manifestations, and as such, it is included under the diagnostic category of schizophrenia, schizotypal, and delusional disorders.

[162] The diagnostic concept of post-schizophrenic depression was discussed by McGLASHAN and CARPENTER (1976) in their paper, AN INVESTIGATION OF THE POST-PSYCHOTIC DEPRESSIVE SYNDROME, published in the Am. J. Psychiatry. Post-schizophrenic depression is a purely defined diagnostic concept, which needs to be distinguished from the REVEALED DEPRESSION (AND DRUG TREATMENT FOR SCHIZOPHRENIA), described by KNIGHTS and HIRSCH (1981), and from AKINETIC DEPRESSION (IN SCHIZOPHRENIA) described by VAN PUTTEN and MAY (1978).

Table XIV

SCHIZOPHRENIA
- Catatonic type
- Disorganized type
- Paranoid type
- Undifferentiated type
- Residual type

MOOD DISORDERS
- Bipolar disorders
  - mixed
  - manic
  - depressed
  - cyclothymia
  - not otherwise specified
- Depressive disorders
  - major depression, single episode
  - major depression recurrent
  - dysthymia
  - depressive disorder not otherwise specified

Classification of schizophrenia and mood disorders in the DSM-III-R.

schizophrenia; and recognizes six different patterns of course.[163] The ICD-10 is the first of the consensus based classifications in which acute and transient psychotic disorders displaying polymorphic clinical pictures, and resembling both, Leonhard's (1957) non-affective, bipolar diagnostic concepts, i.e., unsystematic schizophrenias[164] and cycloid psychoses, and Magnan's (1893) diagnostic concept of transitory delusional psychosis, are separated from the schizophrenias; and, in which schizoaffective

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[163] Course of illness in schizophrenic disorders is separated in the DSM-III-R into subchronic, chronic, subchronic with acute exacerbation, chronic with acute exacerbation and in remission; whereas in the ICD-10, pattern of course is separated into continuous, episodic with progressive deficit, episodic with stable deficit, episodic remittent, incomplete remission, complete remission and other. In the formulation of the patterns of course, consideration was given to the patterns described by MANFRED BLEULER (1941) in his monograph, KRANKHEITSVERLAUF, PERSÖNLICHKEIT, UND VERWANDTSCHAFT SCHIZOPHRENER UND IHRE GEGENSETZIGE BEZIEHUNGEN, and to the patterns described by ARNOLD (1955) in his monograph SCHIZOPHRENER PROZESS UND SCHIZOPHRENE SYMPTOMGESETZE. It should be noted that Bleuler distinguished among seven patterns, i.e., acute onset with a steady course leading to permanent deterioration, chronic simple course leading to a permanent defect, acute onset with a steady course leading to a permanent defect, chronic simple course leading to a lasting defect, acute periodic course resulting in permanent deterioration, acute periodic course resulting in permanent defect and acute periodic course resulting in complete or social cure; whereas Arnold distinguished among 11 patterns, i.e., phasic course of illness with complete cure, phasic course passing over into a shiftlike course, phasic course passing over into a process, shiftlike course passing over into process with exacerbations, primary process course of illness, primary process with exacerbations, mixed psychoses and mixed psychoses passing over into process (Hamilton, 1976).

[164] Both of the diagnostic concepts of Leonhard (1957), i.e., cycloid psychoses and unsystematic schizophrenias, are disorders with a polymorphic disease picture. As such, they correspond to some extent with the ICD-10 diagnostic concepts of acute polymorphic psychotic disorder without symptoms of schizophrenia and acute polymorphic psychotic disorder with symptoms of schizophrenia.

disorder[165] is perceived as a distinctive bipolar disorder, that differs from both, the monomorphic schizophrenic and the monomorphic delusional disorders, and the polymorphic acute and transient psychotic disorders.

In terms of mood (affective) disorders, the other ICD-10 category of disorders, relevant to the structurally determined psychoses reviewed, the distinction between bipolar and unipolar affective disorders, including manic[166], depressive and recurrent depressive disorders, and the separation of the persistent from the other affective disorders are retained.[167] In this respect, the ICD-10 is similar to the DSM-III-R (Table XV).

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[165] There are four distinctive types separated within the schizoaffective disorders in the ICD-10. These are: unipolar manic, unipolar depressive, bipolar mixed and other. The criteria of the unipolar types were adopted from the description of BROCKINGTON, WAINWRIGHT and KENDELL (1980), presented in their paper MANIC PATIENTS WITH SCHIZOPHRENIC OR PARANOID SYMPTOMS, and from the description of BROCKINGTON, KENDELL and WAINWRIGHT (1980), presented in their paper DEPRESSED PATIENTS WITH SCHIZOPHRENIC OR PARANOID SYMPTOMS; and the criteria of the bipolar mixed type were adopted from the description of ABRAMS and TAYLOR (1980), presented in their paper, IMPORTANCE OF SCHIZOPHRENIC SYMPTOMS IN THE DIAGNOSIS OF MANIA, and from the description of MAJ (1985), in his paper, CLINICAL COURSE AND OUTCOME OF SCHIZOAFFECTIVE DISORDERS. The validity of the diagnostic concepts of unipolar and bipolar affective disorders have received substantial support by the results of the family genetic study of Gershon et al. (1982). (Information relevant to the classification of schizoaffective disorders is reviewed and discussed in several papers by MAJ, published in 1984, 1985 and 1986.)

[166] Similar to Leonhard (1957), but in variance with the DSM-III-R, the ICD-10 recognises unipolar manic disorders as an independent group of illnesses. The same disorders in the DSM-III-R are included under bipolar disorders.

[167] The DSM-III-R diagnostic concept of persistent affective disorders was adopted in the ICD-10. Because of this, affective disorders in the ICD-10 are restricted to cyclothymic and dysthymic disorders and do not include hyperthymic disorders.

Table XV

SCHIZOPHRENIA, SCHIZOTYPAL AND DELUSIONAL DISORDERS
- Schizophrenia
  - Paranoid
  - Hebephrenic
- Catatonic
  - Post-schizophrenic depression
  - Residual
  - Simple
  - Other
- Schizotypal disorder
- Persistent delusional disorder[a]
- Delusional disorder[a]
- Other[a]
- Acute and transient psychotic disorder
  - Acute polymorphic psychotic disorder without symptoms of schizophrenia[a]
  - Acute polymorphic psychotic disorder with symptoms of schizophrenia
  - Acute schizophrenia-like psychotic disorder
  - Other acute predominantly delusional psychotic disorder[a]
  - Other acute or transient psychotic episode[a]
  - Induced delusional disorder -- 'Folie a deux'[a]
- Schizoaffective Disorders
  - Manic type
  - Depressive type
  - Mixed type
  - Other

MOOD (AFFECTIVE) DISORDERS
- Manic episode
  - Hypomania
  - Mania without psychotic symptoms symptoms of
  - Mania with psychotic symptoms episode
  - Other
- Bipolar affective disorder
  - Current episode hypomanic
  - Current episode manic without psychotic symptoms
  - Current episode manic with psychotic symptoms
  - Current episode moderate or mild depression
  - Current episode severe depression without psychotic symptoms
  - Current episode severe depression with psychotic symptoms
  - Current episode mixed
  - Currently in remission
  - Other
- Depressive episode
  - Mild severity
  - Moderate severity
  - Severe depressive episode without psychotic symptoms
  - Severe depressive episode with psychotic symptoms
  - Other
- Recurrent depressive disorder
  - Current episode mild severity
  - Current episode moderate severity
  - Current episode severe without psychotic symptoms
  - Current episode severe with psychotic symptoms
  - Currently in remission
  - Other
- Persistent affective disorders
  - Cyclothymia
  - Dysthymia
  - Other
- Other mood (affective) episodes
  - Other single affective episodes
  - Other recurrent affective disorders
  - Other affective disorders

Classification of schizophrenia, schizotypal or delusional disorders and mood (affective) disorders in the ICD-10.

[a] To be discussed in Monograph Two.

Psychopharmacologic Considerations

Introduction of modern psychotropic drugs[168], i.e., lithium (Cade, 1949),[169] chlorpromazine (Delay and Deniker, 1952) and imipramine (Kuhn, 1957),[170] and demonstration of their therapeutic effectiveness,[171] has provided support for the contention, that manic-depressive insanity and dementia praecox (Kraepelin, 1986) are distinctive nosologic categories. It has also provided support

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[168] The term, psychotropic drugs, was introduced by GERARD (1957) in his paper, DRUGS FOR THE SOUL; THE RISE OF PSYCHOPHARMACOLOGY. The term covers the whole spectrum of synthetic and natural compunds which are capable of modifying mental activity and human behavior (Ban, 1969).

[169] The therapeutic effects of lithium in psychiatric patients was first recognised by CADE (1949). His first paper, LITHIUM SALTS IN THE TREATMENT OF PSYCHOTIC EXCITEMENT was published in Med. J. Aust. However, it was Schou (1963), who, approximately 15 years later, gave conclusive evidence, that lithium is a mood stabilizer.

[170] The antidepressant effects of imipramine in depression was first recognised by KUHN (1957). His first paper, ÜBER DIE BEHANDLUNG DERRESSIVER ZUSTANDE MIT EINEM IMINOBENZYLDERIVAT (G 22.355) was published in Schweiz. Med. Weschr. The antidepressant effects of imipramine received further substantiation within a year from Kielholz and Battegay (1958) in Europe and from Lehmann, Cahn and deVerteuil (1958) in North America.

[171] It took approximately eight years from its first psychiatric application until definitive evidence was given that chlorpromazine has therapeutic effects in schizophrenic disorders. Finally, in the United States Veterans Administration Collaborative Studies, it was convincingly demonstrated that chlorpromazine is superior to an inactive placebo in the treatment of both acute and chronic schizophrenic patients (Casey et al., 1960). These findings were further substantiated by the National Institute of Mental Health Psychopharmacology Service Center Collaborative Study Group in 1964.

It took approximately eight years from its first psychiatric application until Klerman and Cole (1965) were able to give definitive evidence that imipramine has antidepressant effects. By pooling the results of 23 published, placebo controlled studies including a total of 1009 patients -- 550 on imipramine and 459 on placebo -- they found that 65 percent of the patients responded favorably to imipramine and 31 percent to an inactive placebo. Corresponding figures in Klein and Davis' (1969) review were 70 percent and 39 percent; and in Angst's (1970) review, 65 percent and 37 percent.

for the notion, that Kraepelin's manic depressive insanity consists of disorders which can be separated on the basis of their polarity (Leonhard, 1957).[172] Furthermore, progress in psychopharmacology has focused attention on the biologic-heterogeneity--in terms of therapeutic reponsiveness to psychotropics--within the traditional diagnostic groups (Ban, 1969).

By now, it is generally recognised that within the diagnostic category of schizophrenia, there is only a subpopulation which responds favorably to pharmacotherapy with antipsychotic drugs[173]; and there are indications that patients with systematic schizophrenia respond less favorably to neuroleptics, than patients with unsystematic schizophrenia. In a clinical study, which included 474 chronic schizophrenics, Fish (1964b) revealed that significantly more patients with the diagnosis of unsystematic schizophrenia (95 % of 123 patients) than patients with the

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[172] It has been argued that results of psychopharmacologic studies are in variance--and not in favor--of the unipolar vs bipolar distinction, because in some studies lithium was found to be effective in both unipolar and bipolar depressive disorders (Coppen et al., 1976, Fieve, Kumbaraci and Dunner, 1976; Prien, Caffey and Klett, 1973; Mendels et al., 1979). Nevertheless, in all the 12 clinical studies in which both unipolar and bipolar depressions responded favorably to lithium, there was a trend for bipolar" patients to show a greater therapeutic response (Mendels, 1976; Mendels et al., 1979). Furthermore, while in the prophylactic treatment of unipolar depressed patients, both lithium and tricyclic antidepressants were significantly superior to an inactive placebo, in the prophylactic treatment of bipolar depressed patients, lithium was significantly superior to tricyclic antidepressants (Schou, 1979; Ban, 1981).

[173] In reviewing 24 placebo-controlled clinical studies including a total number of 3,195 patients (2,127 patients on neuroleptics and 1,068 patients on placebo), Davis (1975) found that 639 (30 %) of the patients from the active drug group and 698 (63 %) of the placebo group relapsed within the investigational period. These findings suggest that 1 (to 2), out of every 3 'schizophrenic patients', remains refractory to prophylactic treatment with neuroleptics (Ban, 1987).

diagnosis of systematic schizophrenia (79 % of 351 patients), showed improvement within the study period. Probably even more important is that in the neuroleptic responsive population, improvement was marked or moderate in more than three times as many patients with the diagnosis of unsystematic schizophrenia (79 %), than with the diagnosis of systematic schizophrenia (23 %).[174] The same as to schizophrenic disorders applies also to bipolar affective disorder, in which only a subpopulation responds favorably to lithium salts[175]; and to unipolar depression, in which only a subpopulation responds favorably to cyclic

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[174] In addition to the report of Fish (1964b) there are at least two other reports (Astrup, 1959; and Astrup et al., 1974) in which, patients with unsystematic schizophrenia were found to respond more favorably to neuroleptics than patients with systematic schizophrenia. Furthermore, in one survey (Ban, Guy and Wilson, 1984; Guy Ban and Wilson, 1985), tardive dyskinesia was encountered significantly more often ($p < .001$) in patients with the diagnosis of systematic schizophrenia (13.3 %), than in patients with the diagnosis of unsystematic schizophrenia (4.3 %).
It should be noted that the contention that schizophrenic patients with positive symptoms (Andreasen, 1983, 1985) and/or schizophrenic patients with the Type I Syndrome (Crow, 1980, 1981) respond favorably to neuroleptics (Angrist, Rotrosen and Gershon, 1980; Johnstone et al., 1978; Lecrubier, 1986), whereas schizophrenic patients with negative symptoms and/or schizophrenic patients with the Type II syndrome remain refractory, could not be substantiated by clinical research (Losonczy et al., 1986; Van Kammen et al., 1986).

[175] Relapse rate with lithium in the prophylactic treatment of 187 bipolar patients, was 35 percent in the clinical study of Schou (1979).
There are indications that within the population of bipolar affective disorder, there is a lithium-refractory subgroup which may respond favorably to anticonvulsants, such as carbamazepine and/or valproic acid (Post, 1990).
It has been observed that some patients with cycloid psychosis, identified by the DCR Budapest-Nashville (Petho and Ban, 1988), but diagnosed as bipolar (affective) disorder by the DSM-III-R, have remained refractory to lithium, but responded favorably to carbamazepine.

antidepressants[176].

[176] Since 25-35 percent of depressed patients do not respond to "cyclic antidepressants" (Angst, 1970; Donnelly et al., 1979, Klein and Davis, 1969) and 30 to 40 percent are placebo-responders, it has been suggested that only 1 (or at most 2 by including placebo-responders) out of every 3 depressed patients respond favorably to pharmacotherapy with antidepressant drugs (Ban, 1987).

Numerous clinical studies aimed at identifying the treatment responsive population to cyclic antidepressants by employing sophisticated statistical techniques (Angst et al., 1976; Bielski and Friedel, 1976; Donnelly et al., 1979; Gurney et al., 1970; Kiloh, Ball and Garside, 1962; Overall et al., 1966, Paykel, 1972; Varga, Angst and Shepherd, 1967; Wittenborn, Kiremitci and Weber, 1973; Woodward, Henry and Overall, 1975). However, findings with "linear regression equations" have remained inconsistent.

It was observed that patients fulfilling Leonhard's (1957) criteria of pure melancholy, identified by the DCR-Budapest-Nashville (Petho and Ban, 1988), responded more favorably to cyclic antidepressants than patients fulfilling Leonhard's criteria of pure depressions.

CONCLUDING REMARKS

Recognition that pathologies of the analytic function of the brain do not necessarily affect the integrating function,[177] and that pathologies of the integrating function have, as a rule little, or no effect, on the analytic function,[176] led to the separation of psychiatry (the discipline which deals with the disorders of the integrating function) from neurology (the discipline which deals with the disorders of the analytic function). However, only with the development of a methodology with the capability to detect that there is pathology of integration,[179] and to identify the results of pathologic integrations,[180] were the prerequisites for the development of a new medical discipline, fulfilled. Since their emergence during the 19th century, the two methodologies, i.e., general psychopathology, (which provides for the detection that there is a pathology in integration), and nosology, (which provides for the identification of the results of pathologic integrations), have grown into a solid foundation of psychiatry.

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[177] The recognition that pathologies of the analytic function do not necessarily affect the synthesizing function implies, that neurologic disorders are not necessarily associated with psychopathologic changes (Feuchtersleben, 1845).

[176] Nyiro (1962) perceived the activity of consciousness in terms of screening and integration. The recognition that pathologies of the integrating function have no effect on the analytic function implies that psychiatric disorders do not necessarily result in detectable neurologic signs.

[179] This monograph is based on the contention that the methodology of general psychopathology, has the capability to detect pathologic integrations. However the analysis provided by general psychopathology is not considered to be sufficient for the identification of any specific psychiatric disease pattern.

[180] This monograph is based on the contention that the methodology of psychiatric nosology, has the capability to identify distinctive patterns, created by pathologic integrations.

Nosologic development began with the identification of organic psychoses (Bayle, 1826), i.e., neuropsychiatric disorders, displayed by irreversible dedifferentiation, the result of primary disintegration, intrinsically linked to neuropathologic changes.[101] It was followed by the identification of exogenous psychoses (Bonhoeffer, 1910), i.e., acute psychoses, displayed by reversible dedifferentiation, the result of secondary disintegration, intrinsically linked to exogenous or endogenous toxic agents (Bonhoeffer, 1910).[102] The formulation of the diagnostic concepts of manic depressive insanity and dementia praecox (Kraepelin, 1896), the former, displayed by pathologic integrations episodically, and the latter by pathologic integrations continuously, opened the path for the recognition of a steadily increasing number of "sui generis psychiatric diseases". A common characteristic of these disorders is that life experience[103] is replaced by pathologic integrations.

Progress in general psychopathology, simultaneously with the development of psychiatric nosology, rendered pathologic integrations increasingly accessible to direct analysis. This, in

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[101] Neuropsychiatric disorders will be discussed in detail in Part Two of this series. They are perceived as the result of pathologies of the analytic function, which are displayed by their effect on the integrating function.

[102] Exogenous psychoses will be discussed in Part Two in this series. They are perceived as pathologies in which an exogenous and/or endogenous toxic agent exerts a transient effect on the screening function of consciousness.

[103] Sui generis psychiatric disorders are perceived as distinctive patterns generated by pathologic integrations. In case of sui generis psychiatric disorders, the pathologic patterns preclude the physiologic-adaptive interplay between the individual and his/her environment.

turn, yielded to the recognition of a steadily increasing number of nosologic patterns.[104] Considering, that delusions are the prototype psychopathologic symptoms, and delusional disorders are the prototype nosologic patterns, in Monograph Two, the classification of delusional disorders will be reviewed and discussed.

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[104] Each sui generis psychiatric disorder is perceived as a distinctive clinical pattern; whereas all the different neuropsychiatric disorders result in one and the same clinical pattern.

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