CLASSIFICATION OF PSYCHOSIS

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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 recognized that validation of diagnostic hypotheses is one of the most important steps in the development of nosologic concepts[1]. In spite of this, there is no consensus with regard to acceptable validation criteria for mental illness[2].

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

[1] 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).

[2] 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 SHIZOPHRENIA. Such external validators include family history, demographic correlates, biological and psychological tests, environmental correlates, biological and psychological tests, environmental risk factors, concurrent symptoms, treatment response, diagnostic stability and course of illness (Kendler 1990).

(1850-51) in his lectures at Salpetriere in Paris.[3] 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) symptoms, with full remission between episodes.[4]

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[5]; and Leonhard´s diagnostic criteria for manic-depressive disease were adopted with some modifications by Perris (1074) in his diagnostic criteria of bipolar affective disorders[6].

Results of family-genetic studies are in support of the contention that bipolar affective disorder is a genetically meaningful nosologic category.[7] Mean concordance rates of "bipolar affective disorder" in "monozygotic-identical cotwins" were found to be

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[3] The diagnostic concept of folia circulaire first appeared in J. P. Falret´s Lecons a l´Hospice de la Salpetriere, 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 FOLIR A DOUBLE FORME, presented the same diagnostic concept in a more comprehensive manner.

[4] 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 in this final formulation of manic-depressive insanity, in the monograph, DIAGNOSTIC CRITERIA FOR SCHIZOPHRENIC AND AFFECTIVE PSYCHOSES, of BERNER ET AL. (1983).

[5] 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.

[6] 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 sub forms. 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 generically distinctive conditions, because in the families of patients with bipolar II disorder the incidence of bipolar II disorder was 1%. 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% by Stentedt (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% 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.

[7] 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).

as high as 72[8] and 76%[9] 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[10].

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 linkage analysis[11] 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, 1938),[12] (2) a gene linked with red-green color blindness

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[8] Goodwin and Guze´s (1989) figure of 72% concordance rate of "bipolar affective disorder" in "identical twins" is based on pooled data from the nine twin studies reviewed by ALLEN (1076) in his paper, TWIN STUDIES AND AFFECTIVE ILLNESS.

[9] Tsuang and Vandermey´s (1980) figure of 76% 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" rages from 50 to 93%.

[10] 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."

[11] 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 sequenced" 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 the proximity to an actual disease gene," which the "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 FUTURA 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 market 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%, but when there is linkage, this fraction approaches zero."

[12] 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

located on the long arm of the X-chromosome and/or a gene linked with the blood group labelled X, located on the short-arm of the X-chromosome (Winokur and Tanna 1969; Mendlewicz, Fleirss and Fieve 1972; Fieve, Mendlewicz and Fleiss 1973);[13] (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 arm of chromosome II (Egeland et al. 1987),[14] and (4) a gene linked with the histocompatibility locus antigen (HLA) complex located on chromosome 6 (Mathysse and Kidd 1981; Weitkamp et al. 1981)[15]. However, the fact remains that replication of findings in genetic-transmission studies have invariably failed. Despite 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 study sample by bipolar disorders, other than manic-depressive disease, e.g., cycloid psychoses, unsystematic schizophrenias.

Dementia Praecox

GENES AND THE MIND pointed out "the issues of x-linkage in mood disorders is not by means settled. Numerous studies have found example of ill father and ill son pairs."

[13] 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 moos disorder being linked to both color-blindness and the X, 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 off 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 79%) of detecting linkage even if only one quarter were linked, we in Bethesda have definitively excluded linkage."

[14] Egeland et al. (1987), based on 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 Southers Sandinia. 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.

[15] 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 (19083).

The origin of Kraepelin´s (1899) nosologic concept of dementia praecox was in the diagnostic concept of demence precoce, first described by Morel in 1852.[16] 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."[17]

By replacing the term dementia praecox with the term schizophrenia and redefining schizophrenia as a "group of 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[18]. His fundamental, or basic symptoms[19] 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 rank symptoms[20].

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[16] MOREL´S first description of the disorder was in his ETUDE CLINIQUES, published in 1852-1853. However, it was only seven years later in 1860, in his TRAITE DES MALADIES MENTALES, that he introduced the term "demence precoce."

[17] 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 paranoids," "flighty, silly deterioration" and "dull, apathetic dementia."

[18] The term "schizophrenia" was introduced in the title of BLEULER´S monograph, DEMENTIA PRAECOX ODER DER GRUPPE DER SCHIZOPHRENIES, 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 SHIZOPHRENIAS, by International University Press in New York.

[19] Bleuler (1911) considered the fundamental or basic symptoms of schizophrenia, such as loosening of associations, inappropriateness of affect, ambivalence 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 distinguished between primary and secondary symptoms pf 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.

[20] KURT SCHNEIDER´S "first rank symptoms" were first published in 1957, in his paper PRIMARE UND SECUNDARE SYMPTOME BEI SHIZOPHRENIE. 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 exclusive for schizophrenia.

Results of "family-genetic" studies are in support of the contention that schizophrenia is a genetically meaningful[21] 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%)[22] (Slater and Cowir 1971).[23]

Supportive also are the findings that the risk to develop 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%)[24] (Shields and Slater 1967).[25] 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),[26] 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 population (Altschuler 1956)[27], 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

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

[22] The risk figure of 0.86% of 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% ranging from 0.42% in Germany to 1.25% in Sweden. In Switzerland it is 2.38%, but this higher rate is almost certainly due to the influence of Bleuler´s concept of schizophrenia (Hamilton 1976).

[23] The figures relevant to the rick 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).

[24] Same sex fraternal-twin pairs have similar sex chromosomes and therefore they are genetically more similar tan 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.

[25] The risk figure 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).

[26] 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%).

[27] 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.

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% (Essen-Moller 1941), and identified by strict criteria of schizophrenia, ranges from 6 (Tienari 1963) to 50% (Luxenburger 1928), with a pooled concordance rate of 45.6% (Tsuang and Vandermey 1980).[28]

These figures are not sufficiently high[29] to provide support for the contention that schizophrenia is a genetically valid concept[30], and suggest, that what is diagnosed as schizophrenia, consists of two or more genetically distinctive disorders.[31]

Unsystematic and Systematic Schizophrenias

Genetic research in schizophrenia led to a re-evaluation of the unitary nosologic concept[32] of dementia praecox. This, in turn, "based on current knowledge about age and

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[28] 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), Rosanoft 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).

[29] 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% when both twins were right-handed, whereas it as 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).

[30] 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)

[31] 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; 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. 1872, 1975) can account for the observed frequency of schizophrenia in first degree relatives of schizophrenic probands. In keeping also are the findings of Stewrt, Debray and Caillard (1980), who, on the basis of the recognition that direct likelihood comparison 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.)

[32] 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 SCHIXOPHRENIE 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

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 Tsuag and Vandermey (1980) to separate within schizophrenia organic and true (i.e., sui genesis) schizophrenic disorders; and within the true schizophrenic disorders, atypical and typical forms.[33]

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. Similar to Kleist, Leonhard maintained that these two distinctive categories of schizophrenic psychoses are unrelated to each other and are 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.[34]

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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his monograph on RECENT ADVANCES IN THE BIOLOGY OF SCHIZOPHRENIA, published in 1973).

[33] One of the early dichotomies within schizophrenic disorders, is the distinction between schizophreniform and schizophrenic psychoses. It was put forward by LANGFELDT (1937, 1039) 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.

[34] 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 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 course as well are fully different. The systematic 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% of the patients with systematic schizophrenia had relatives hospitalized with endogenous psychoses, whereas 37% of the patients with unsystematic schizophrenia had relatives hospitalized with such diagnoses.[35] Corresponding figures in Leonhard´s (1979) Berlin sample,[36] were 17.5% and 70.2%;[37] and in Astrup, Fossum and Holmboe´s (1962) Oslo sample, were 14% and 36% respectively.[38]

Interpretation of findings in family-genetic studies of 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, [39] e.g., by the inclusion of patients with cycloid psychoses (with a disease rate of 4.7% in the siblings) among the unsystematic schizophrenias.[40]

Cycloid Psychoses

The origin of Leonhard´s (1957, 1961, 1967) diagnostic concept of cycloid psychosis[41] is in the diagnostic concepts of autochthonous degeneration psychosis and

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[35] 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.

[36] Information on the Berlin simple was first reported by TROSTORFF (1975) in her paper VERLAUF UND PSYCHOSE IN DER VERWANDTSCHAFT BAI DEN SYSTEMATISCHEN UND UNSYSTEMATISCHEN SCHIZOPHRENIEN UND 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).

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

[38] In their Norwegian simple, 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 percentage suffer from systematic schizophrenia, was not impressive (i.e., 52% and 48% respectively).

[39] 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.

[40] 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.

[41] 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

cycloid marginal psychosis of KARL KLEIST (1921, 1928), presented in his papers, AUTOCHTHONE DEGENERATION PSYCHOSEN and UBER ZYKLOIDE, PARANOIDE UND EPILEPTOIDE PSYCHOSEN UND UBER DIE FRAGE DER DEGENERATION PSYCHOSEN[42]. They refer to a category of mental disorders with a cross-sectional psychopathology similar to that seen in the unsystematic schizophrenias,[43] and a longitudinal course of illness similar to that seen in the phasic psychoses, e.g., manic depressive disease.[44]

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 emphasis in the diagnosis of cycloid psychosis, from paranoid anxiety and/or motility extreme, to acute onset and polymorphic (multiform) symptomatology with confusion.[45]

(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 psychoses (Leonhard, 1934), resulted in the present concept of cycloid psychosis, which includes confusion, anxiety-happiness and motility 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: Diagnoses and Heuristic Value, published in 1982.

[42] Many of the diagnostic concept 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.

[43] 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.

[44] LEONHARD in his lecture at the Royal Edinburgh Hospital for Nervous and MANETAL 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 and 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.

[45] 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 mood syntonic hallucinations which are congruent with the mood state, (c) motility disturbances (hypo-or hyperkinesia), (d) occasional episodes of states of ecstasy, and/or

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 rick 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 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 schizophrenias.[46]

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% respectively) 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).[47]

However, the strongest support in favor of the contention that cycloid psychosis is a genetically meaningful[48] nosologic category, was given by the findings of the high "nosologic homotypy" for cycloid psychosis. Accordingly, in Ungvari´s (1985) sample, 57%, and in Perris´ (1974) sample, 77%, of the parents and siblings of patients with cycloid psychosis, who were affected by the endogenous psychosis, suffered from cycloid psychoses[49]

(e) pananxiety. In terms of severity, it is characterized by psychotic or occasionally psychotic manifestations (with 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.

[46] 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.

[47] It was noted that in Leonhard´s (1979) Berlin sample morbidity risk for endogenous psychosis among the parents of patient with anxiety-happiness psychosis was 6.7%, 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%).

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

[49] 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% 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).

Phasic Psychoses

The term, phasic psychoses, was first used by EDDA NEELE in het 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.[50]

With consideration to the contributions of Lange (1897) and Schou (1927), Leonhard (1957) divided phasic psychoses into two major categories, i.e., 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 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). Furthermore, with consideration to Kleist's (1943, 1947) contributions[51], 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[52] within the affective disorders (Angst 1966; Peris 1966; Winokur and Clayton 1967).[53] In his Berlin sample, Leonhard (1979) found that the frequency of endogenous psychoses in both, the siblings and the parents of patients with bipolar manic depressive disease was considerably higher (10.8% 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 euphoria (3.9% and 4.6%, respectively). He also found that while the number of phases was greater in bipolar (4.2) than in unipolar

[50] 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).

[51] 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."

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

[53] 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 differential 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."

disorders.[54] 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[55] and 3-methoxy-4-hyfrexyphenylglucol (MHPG) concentrations in the urine.[56]

While findings in twin pairs, concordant for mood disorder, showed that 81% of the pairs were also concordant for polarity, other family-genetic study data on patients with bipolar-affective-disorders was not restricted to bipolar, but included also unipolar – affective – disorders (Tsuang and Vandermey, 1980)[57] 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 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).[58] Because of this, in spite of all supporting data, the controversy, regarding the distinctiveness of unipolar and bipolar affective disorders cannot be considered as resolved.[59]

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[54] 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 depression; and 2.9 in the pooled manic population of unipolar disorders, i.e., pure mania and pure euphoria.

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

[56] 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.

[57] 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-Rubin (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), Goerzl et al. (1974), Gershon et al. (1976) and James and Chapman (1976).

[58] A detailed review of findings in a series of validation studies regarding the unipolar-bipolar distinction was presented by AKISKAL (1983) in his chapter in 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 Mcnney (1975), Depue and Monroe (1978), Gershon (1978) and Dunner (1980).

[59] 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 conclusion were reached by Smeraldi, Negri and Melica (1977) and Vandermey (1980) maintained that generically, unipolar and bipolar disorders are two separate illnesses.