Controversies in Depression,

or Do Clinicians Know Something After All?

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Essential Papers on Depression

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In two extremely lucid efforts, Kendall has reviewed both the historical background of the controversies over classification of depressive illnesses as well as the contemporary viewpoints (Kendall, 1968 & 1976). To now attempt a dreary recounting of something like Kraepelin noted, Lange delimited, Gillespie observed, Mapother challenged, Buzzard responded, and Lewis asserted would be reminiscent of the biblical chronicles which noted that Elezarb begat Phinebas, Phinebas begat Abisua, Abisua begat Bukki, and Bukki begat Uzzi, etc. Further, this would not solve the issue. Kendall presents nine different contemporary classifications, mainly

based on clinical background. To these we may add others that would be more biological. For instance, some suggest that abnormalities in excretion of MHPG might be used to separate depressions. Response to lithium could separate depression. Response to lithium and prevention of illness with lithium could separate depressions. Abnormal nonsuppressor status in the dexamethasone suppression test may be useful in classification, as might 5-HIAA in spinal fluid. All of these biological measures could be related to an entire new set of classifications. The methods that are used vary from simple clinical description and follow-up to cluster analysis, factor analysis, and discriminant function analysis.

However, if we may be allowed to switch simile to metaphors in midstream, we would like to cut the Gordian knot. What seems necessary now is to determine whether any particular

classification may be validated by its relationship to other classifications. In other words, if two classifications were compared to each other, would they have a great deal in common? If so, it would indicate some validity in both of them, even though the starting points of the classifications were different.

Clinicians have considered two major groups of depression, endogenous-psychotic and reactive-neurotic. The endogenous-psychotic group shows such symptoms as severe depression, social incapacity, feelings of worthlessness, retardation, terminal insomnia, anorexia, and marked suicidal intent. The reactive-neurotic group is typified by a less severe depression, a neurotic or stormy life prior to the depression, and a relationship to precipitating factors. In fact, the term “reactive” is somewhat misleading. It is fairly clear from the superb studies of Clayton and her colleagues that

even a simple bereavement is related to a reactive depression in fully a third of widows and widowers (Bornstein, et al. 1973). Bereavement is a normal response to a death of a close relative or friend. Although it manifests itself by a definable depression and is associated with a precipitating factor, there is no reason to believe that people who suffer from a bereavement depression are those with a stormy history. Therefore, it will not be considered further in this chapter.

Klerman et al. have presented the criteria for neurotic depression and what is important is the fact that the definition varies from study to study (Klerman et al., 1979). They point out that neurotic depressions may be defined six different ways. They may be less socially incapacitating or they may be nonpsychotic (i.e., no delusions or hallucinations) or they do not present such endogenous symptoms as early morning

awakening, weight loss, retardation, or they may follow a stressful event (in which case they would be considered reactive), or they may be a consequence of a longstanding maladaptive personality pattern (i.e., a stormy personality), or finally they may be the result of unconscious conflicts. In any case, they should be considered as a mixed group when clinicians make the diagnosis. The fact that there is no great precision in the diagnosis does not mean that there may not be a kernel of truth in the separation of endogenous-psychotic form of depression from the reactive-neurotic form. In this paper, we will approach this clinical separation by evaluating it against a classification from an entirely different viewpoint, namely a separation on the basis of family background. Although this deals with an old controversy in psychiatry, it is still an active one, and one which is very meaningful to clinicians.

Finally, we will present data on a new controversy in depression which is currently waiting in the wings for a major appearance. This controversy has to do with the diagnosis of depression in the community versus the diagnosis in a psychiatric setting.

THE DIFFERENTIATION OF ENDOGENOUS-PSYCHOTIC FROM NEUROTIC-REACTIVE DEPRESSION

At the outset, let us state that we will not deal with bipolar patients, only unipolars. Further, there is a problem with the differentiation between primary and secondary depression. Secondary depression is a simple depression that occurs in the context of another psychiatric illness, such as alcoholism or antisocial personality, hysteria, or anxiety neurosis. It is entirely conceivable that some patients called reactive-neurotic in fact have secondary depression and

their primary diagnoses would be some other psychiatric illness. For the purposes of the present discussion, we will consider only reactive-neurotic patients who have primary depressions.

First, we need to look at circumstances which predate the depression for which the patient is treated. There are only three possibilities for this: precipitating factors, premorbid personality, and a positive family history. Some data exist on the follow-up and perhaps these data might also separate the two groups. It is conceivable that some circumstances which involve the use of laboratory tests might separate the two groups and we will explore that. After we deal with that in the reactive-neurotic, endogenous-psychotic dichotomy, we will examine another method of classification, namely a familial classification, and note any overlap in the findings.

THE CHARACTERISTICS OF NEUROTIC DEPRESSION AND ENDOGENOUS DEPRESSION

In a systematic study of symptoms and other types of clinical data, Kiloh and Garside (1963) looked at a variety of items. They evaluated 92 patients who had clinical diagnoses of neurotic depression or endogenous depression. Table 1 shows a variety of clinical features evaluated in the Kiloh and Garside study that correlate with one or the other diagnosis at a significant level ($p < 0.05$).

Table 1. Some clinical features that correlate with diagnosis in decreasing size of correlations

Neurotic depression	*Endogenous depression*
Reactivity of depression	Early awakening
Precipitation	Diurnal variation
Self-pity	Retardation
Hysterical features	Concentration difficulties
Immaturity	Significant weight loss
Inadequacy	Previous episodes
Irritability	
Hypochondriasis	

The simple presentation of these features that were correlated with the clinicians' diagnoses does not prove that the two illnesses exist. What it may prove is the certain features may have been uppermost in the minds of the clinicians when they made these diagnoses and these features were the found in retrospect. To assume that this proves the existence of these symptoms as separate entities would be circular. The authors then subjected the data to a factor analysis. Two

factors were extracted. With further statistical manipulation, it was found that the data could not be produced by a single depressive condition but had to be explained by the presence of two separate conditions. In another publication, Carney et al. examined a group of endogenous and neurotic patients and subjected the clinical features to a multiple regression analysis (Carney et al., 1965). The distribution of the scores were shown to be bimodal rather than unimodal and this also suggested the presence of two distinct illnesses. Kendall published material using discriminant function analysis and was unable to find the same kind of bimodality; he suggested a continuum rather than separate illnesses (Kendall, 1976).

If we look at Klerman's description of the various ways in which a diagnosis of reactive-neurotic depression is made, two major points

stand out. These are relevant to the presence of precipitating factors and the presence of a premorbid stormy personality. Such features are seen in Table 1. If one peruses Kendall's material, it is clear that such items as childhood neurotic traits, previous hysterical symptoms, previous subjective tension, always ailing, and previous demonstrative suicidal attempts are more likely associated with the diagnosis of neurotic depression than endogenous depression. This is also true as regards precipitating factors, though in both groups, endogenous and neurotic, a majority of patients have precipitating factors (Kendall, 1976). However, these clinical features may have been simply the reason for the clinician's diagnosing neurotic depression.

Paykel et al. have shown some relatively weak but significant correlations between life event scores and symptoms in depression, as well as

neuroticism scores on the Maudsley Personality Inventory and depressive symptoms (Paykel et al., 1971). Anxiety is positively correlated with the neuroticism scores, as are irritability, obsessional symptoms, and feelings of helplessness. These would be symptoms that would be seen in a reactive-neurotic type of depression. As regards recent life events, these are correlated positively with irritability but negatively with diurnal variation, anorexia, and retardation. The problem seems simple enough. In any large group of patients who are called reactive-neurotic depressive, the two defining characteristics of precipitating factors and a stormy life background will be found. However, it is hardly an invariable finding. Such circumstances are also found in patients who are called depressed for endogenous reasons.

Should one want to determine which is the

better of the two criteria, either precipitating factors or a stormy life-style, some data on treatment might be useful. DeCarolis presented material on ECT in 437 patients who suffered from depression (Avery & Lubrano, 1979). Electroconvulsive therapy is more effective in endogenous depression than reactive-neurotic depression. After ECT in the total group of depressives, 72% were considered as improved. On the other hand, of 31 patients who had reactive-neurotic depressions, only 26% were improved as opposed to 85% of the patients who were considered to have endogenous depressions. What is most interesting, however, is that the precipitating event used as a means of separating patients was less useful than the diagnosis of reactive-neurotic depression. Thus, of 111 patients with precipitating events, 62% were considered improved versus 84% of 79 patients

with no precipitating event. Clearly, the diagnosis of reactive-neurotic depression is a more useful separator, at least as regards response to treatment, than is the simple assessment of whether a precipitating event was associated with the depression. Presumably, the stormy life-style was more useful as a predictor than the presence of life events.

Of some interest is the study by Mendels who looked at a group of 100 depressed patients and noted that the presence of such reactive symptoms as neurotic traits in childhood and adulthood, precipitating factors, inadequate personality, and emotional liability separated patients into two groups better than such endogenous items as a family history of depression, feelings of self-reproach, diurnal variation, delusions, and early morning awakening (Mendels, 1968). He also found that there was a poor clinical response to

electroconvulsive therapy if the patient showed neurotic traits in childhood, precipitating factors, inadequate personality, and emotional lability. There was a good response to ECT if the patient showed psychomotor retardation.

Probably the most important set of studies in differentiating the endogenous psychotic from the reactive-neurotic groups are the follow-up studies. In a 5-7-year follow-up of 104 cases, Kay et al. showed that immediate recovery was more likely in the endogenous than in the neurotic group ($p < 0.05$) (Kay et al., 1969). In the follow-up, though there are clearly more readmissions for the endogenous group, the neurotic group is more likely to show prolonged ill health. This is an interesting difference and would suggest a more episodic course with recovery and exacerbations in the endogenous group and a more constant course of morbidity in the neurotic group. A

course of prolonged ill health was to some extent predicted by “neurotic” syndrome and somatic complaints. Table 2 presents these data. Paykel et al. also have reported on a follow-up, in this case 10 months (Paykel et al., 1974). In general, endogenous depressives showed a better prognosis. However, the findings were somewhat different from those of the previous study. Patients with remissions and subsequent relapses in that short period of time tended to be more neurotic than patients with remission and no subsequent relapse who tended to be more endogenous. In this study, however, relapse did not necessarily mean readmission. Also, the difference in length of follow-up may not make the studies comparable. Though not all studies are consistent in their results, it seems fairly clear that some patients come into the hospital with a lot of precipitating factors and a life history of stormy

problems. Thus, there is some reason to believe that there are a number of patients with these features who may be different from the endogenous group; however, there is a considerable overlap in symptomatology. The question that arises is whether such findings, though not perfect, indicate a meaningful differentiation of specific illnesses within the large rubric of depressive illness.

Table 2. Outcome in patients with "endogenous" syndrome versus those with "neurotic" syndrome

	"Endogenous" syndrome	*"Neurotic" syndrome*
n	31	
Recovered on leaving hospital	22 (71%)	12 (31%)[b]
Readmission in follow-up	15 (48%)	9 (23%)[a]
Prolonged ill health	7 (23%)	16 (%)

[a] $p < .05$

[b] $p < 005$

CROSS VALIDITY USING A DIFFERENT METHODOLOGY FOR SEPARATION OF DEPRESSIVE

ILLNESS

There is another way to classify patients who enter the hospital with primary unipolar depressions, namely, by family background. Figure 1 shows a separation of primary and secondary depressions. Secondary depressions are those depressions which occur in the context of another psychiatric illness, such as alcoholism, antisocial personality, anxiety neurosis, and obsessional neurosis. Because secondary depressions may show a “neurotic” background, it is likely that in many studies they overlap to some extent with reactive-neurotic depressions.

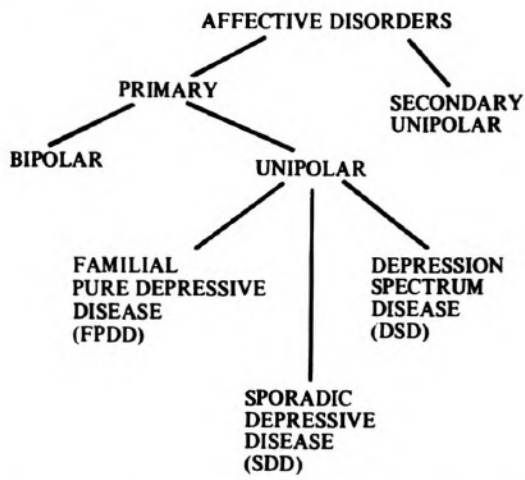

Figure 1. Classification of primary and secondary depressions.

The unipolar primary depressives suffer one or more depressions and may be divided on the basis of family background. There are three types. One of these is depression spectrum disease (DSD) which is an ordinary depression occurring in a person who has a first-degree family member who shows alcoholism and/or anti-Social personality. Another first-degree family member may or may not show depression. The second type is familial

pure depressive disease (FPDD) which is an ordinary depression in an individual who has a first-degree family member with depression but no alcoholism, antisocial personality, or mania. The third type is sporadic depressive disease which is an ordinary depression in an individual who has a negative family history for alcoholism, antisocial personality, depression, or mania.

The major differentiating factor in these three groups is age of onset which, for the sporadic group, is far older, close to 10 years, than in either the depression spectrum or the familial pure depressive disease group (Winokur et al., 1978). There is a problem with the definition of an illness such as sporadic depressive disease which is made on the basis of an absence of some specific family history. It is quite possible that there are a number of false negatives in this group; and, therefore, though the group is useful and should be

separated from the other two groups, it still has to be studied as an illness on its own. However, it is possible to compare the familial pure depressive disease with the depression spectrum group.

When this is done, there are some interesting differences. The age of onset in the two groups is similar. However, if one looks at a group of female patients and compares the ones with depression spectrum disease to those with familial pure depressive disease, it is clear that there is a larger set of personal problems in the group with depression spectrum disease (Van Valkenburg et al., 1977, Winokur et al., 1978). Table 3 presents the clinical features that are significantly different between the groups. What is interesting is that the one symptom difference which separates them is one that has usually been considered associated with endogenous depression, namely loss of interest in usual activities. This is seen more

frequently in the familial pure depressive disease group. On the other hand, marital and sexual problems which would indicate neurotic difficulties in the past are more frequently seen in depression spectrum disease. The data in Table 3 should be compared with those in Tables 1 and 2 which showed differences between reactive-neurotic depression and endogenous-psychotic depression. The findings are quite similar. Of importance is the fact that although stormy life-styles separate DSD from FPDD, precipitating factors were seen equally in both groups.

Table 3. Significant differences between female depression spectrum disease and familial pure depressive disease patients

Clinical features	*Depression spectrum disease*	*Familial pure depressive disease*
Loss of interest in usual activities	61%	80%
History of sexual problems	32%	15%
History of divorce or	20%	8%

separation		
Lifelong irritability	20%	8%
Previous episodes of depression/person	0.66	1.12
At least one relapse in depression at follow-up	21%	49%
Subsequently hospitalized	26%	44%
Final clinical diagnosis of reactive depression	32%	17%

Table 3 also shows follow-up material in two groups of women, one with depression spectrum disease and one with pure familial pure depressive disease. The patients with familial pure depressive disease are more likely to have had episodes prior to entering the hospital for an index admission and in the course of the follow-up are more likely to have had subsequent hospitalizations. Thus, the data look rather similar to the material in the Kay et al. (1969) follow-up study.

In an attempt to look at these kinds of problems in a new group, we have examined

patients with depression spectrum disease and familial pure depressive disease that have been collected locally at the University of Iowa as part of an NIMH Collaborative Depression Study. Table 4 shows these preliminary data. There are more marital problems among the group with depression spectrum disease than one sees in the familial pure depressive disease group. In fact, if one looks at the mean number of symptoms in the two groups together, one finds that there is 3.0 martial problems in the combined groups. Thirty-six percent of the familial pure depressives have greater than three problems, whereas 61% of the depression spectrum disease patients have greater than three marital problems. Of course, this only deals with those people who are currently married. Both groups contain the same number of people separated and divorced, 31%; but as the depression spectrum patients are 7.5 years

younger at index, they have had far less time to go through and accumulate separations and divorces.

Table 4. Preliminary data on differences between depression spectrum and familial pure depressive disease patients

	DSD	*FPDD*
n	35	22
% Female	77	55
Age at index	32.5	40.0
Proportion separated or divorced of those ever married	31%	31%
Proportion with greater than three marital problems of those currently married	61%	36%

It would seem clear that many of the qualities that are seen in neurotic depressive patients are also seen in depression spectrum patients and many of the qualities seen in endogenous patients are seen in familial pure depressive disease patients. The thing that is interesting is that the separation adds another dimension to classification. It is done by the presence of the family history rather than by the presence of

specific clinical symptoms.

FURTHER DATA SHOWING AN ASSOCIATION BETWEEN FAMILIAL SUBTYPING AND THE ENDOGENOUS-NEUROTIC CONTINUUM

Most studies of the endogenous-psychotic, reactive-neurotic dichotomy, when they have used family history for a separation, have only looked at family history of depression. What seems important is to look at the other possibility which is the family history of alcoholism. In Table 3, a clinical diagnosis of reactive depression is shown to be related to depression spectrum disease which is diagnosed because a person has a family history of alcoholism. In this study of 289 depressed women, 104 had a family history of alcoholism and showed a clinical diagnosis of reactive-neurotic depression in 32%; of 184 with a lack of familial alcoholism, 15% were diagnosed as reactive-neurotic depression ($x^2 = 10.7$, d.f. = 1, $p <$

0.005) (Winokur et al., 1978). Table 5 shows the results of another study in which the family history of alcoholism was compared in "reactive" depression versus manic-depressive disease (Winokur & Pitts, 1964). Significantly more alcoholism was found in the sibships of reactive depressions. This finding once again makes one believe that there is a clear overlap between depression spectrum disease and reactive-neurotic depression.

Table 5. Family history of alcoholism in depression

	Reactive depression	*Manic depressive and psychotic depression*
Probands (n)	75	212
Alcoholic fathers	13%	9%
Alcoholism in sibships	11%	3%

Perhaps the most important support for an association between the two classification systems are the dexamethasone test data. Table 6 shows a

series of findings on different diagnoses. Carroll has presented data separating endogenous depressives from neurotic depressives; abnormal dexamethasone nonsuppressor status is seen in endogenous depression but a normal status is seen in reactive depression (1978). Schlesser et al. have looked at the same test but used a familial classification (1980). The familial pure depressive patients are likely to show an abnormal nonsuppressor status whereas the depression spectrum patients are usually quite normal as regards their suppressor status. Again, this shows a real association between the old clinical endogenous-neurotic classification and the familial classification of patients.

Table 6. Results of dexamethasone suppression test in different types of unipolar depressions

	n	*% abnormal (nonsuppressors)*
Endogenous	35	51
Depressive neurosis	18	0

Familial pure depressive disease	50	76
Depressive spectrum disease	41	7

There are few data on treatment and subclassification but it is interesting to note that depressives with one or more episodes prior to the index admission are far less likely to respond with marked improvement to antidepressant drugs than those admitted for the first time (Avery & Winokur, 1977). In a sense this is opposed to the clinical wisdom which indicates that patients with endogenous depression (who may have more episodes than neurotic depressions) are the ones who respond to tricyclics; in fact, what this may indicate is that patients with reactive-neurotic or depression spectrum disease might be somewhat more likely to respond to the antidepressant drugs. This, of course, needs to be investigated further. In any event, on the basis of similarities in stormy premorbid life-style, course of illness, a

family background of alcoholism and dexamethasone suppressor status, depression spectrum disease and reactive-neurotic depression appear to overlap, as do endogenous-psychotic depression and familial pure depressive disease. This is of special interest in that it is possible to find some validation of an old classification by the use of a new classification. The common background of alcoholism in reactive-neurotic depression and depression spectrum disease suggests the possibility of a genetic factor in this type of illness.

AN EMERGING CONTROVERSY IN DEPRESSION

It is clear that we are identifying a large number of patients in the community who meet lenient research criteria for depression, either major or minor depression (Weissman & Meyers, 1978). It seems unlikely that this is all one illness.

An evaluation of a normal control group in Iowa shows also a large amount of illness in the population. This is noted in Table 7. About 24% of the population is likely to suffer or have suffered from some kind of primary depressive illness which meets the same research criteria. Today, it is inconceivable that we would diagnose anybody as depressed who did not meet reasonable research criteria, but it is possible that many people who do, do not necessarily have a depression or at least the same kind of depression as those patients who are hospitalized for a depressive illness.

Table 7. Affective disorders in a control population in Iowa

	n	*%*
People examined personally	85	
Diagnosis		
Bipolar	2	2.4
Major depressive disorder, primary	16	18.8
Minor depressive disorder	2	2.4

Total	20	23.5

The questions which arise are whether these patients need to be treated, whether all of them have a similar kind of illness, and for that matter whether they have any illness at all. To obtain an answer, we have used a relative ratio methodology. It is possible to use information from a family study and family history study to assess this. In the Iowa 500 about twice as many relatives of depressives and manics showed an affective illness as was found in a control population (Table 8). However, about eight to nine times as many of the deceased relatives in the families of the affectively ill index cases showed a chart for hospitalization for severe psychiatric illness. Though a higher proportion of relatives of affective disorder probands than control relatives was deceased, this did not account for the increased ratio. Further, in Fig. 2 which shows

these ratios graphically, we also find that in a follow-up five to six times as many affectively ill probands died by suicide as did the controls. Thus again the relative ratio comparison favors a difference between the depressive in the population versus the depressive who is hospitalized. What I am suggesting is that the question of severity and the question of medical treatment may really be tapping an entirely different set of people than are found by the simple examination which leads to meeting research criteria. It may be that the community separates out seriously ill people, forces them into treatment, and that these are qualitatively different from those patients who are simply diagnosed in the general population. If severity were not of importance, why would the ratio of deceased relatives with psychiatric records (relatives of ill probands: relatives of controls) be

a more discriminating measure of familial pathology than the personal examination data? Neither increased mortality in affectively ill people nor differential emigration rates from the state account for these differences (15,16,21). Further, the suicide differences are also indicative of the importance of severity.

Table 8. Relative ratios (clinical affective disorder: controls) on two measures of family psychopathology

	Personal exam measure			*Psychiatric records deceased relatives*	
	Relatives at risk	Relatives with mania or depression	Ratio	Deceased relatives	Number of records
Controls (n = 160)	344	26 (7.6%)	1.7	332	2 (0.6%)
Manic + depressives (n = 325)	500	65 (13%)		918	47 (5.1%)

Comparisons: controls versus manics and depressives

Personal exam measure ($x^2 = 5.72$, d.f. = 1, $p < 0.025$)

Psychiatric records measure ($x^2 = 12.04$, d.f. = 1, $p < 0.001$)

Deceased relative/control = 2.0, deceased relative/affective disorder patient = 2.8

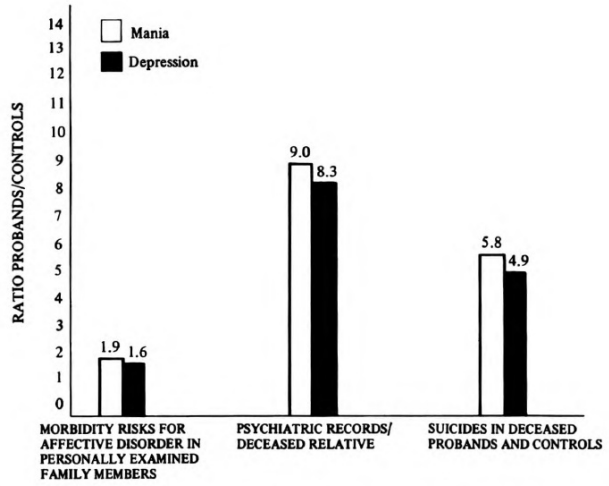

Figure 2. Relative ratios, probands to controls, on measures of serious family psychopathology and suicide.

What do these ratios indicate? They support the idea that severity as defined by treatment, particularly treatment in a mental hospital, and the outcome by suicide defines an entirely different population from that which is obtained by patients meeting the criteria for depressive illness in the community. If this statement were not so, we would expect the ratios for suicide in

follow-up and psychiatric records per deceased relative to be equal to the ratios of morbidity risks for affective disorder in personally examined family members. That severity as defined by treatment and suicide outcome is important should not surprise us. The studies on bereavement have already suggested this. Bereavement frequently manifests itself similarly to clinical depression, but it does not necessitate treatment. It is simply not enough to accept the clinical picture as a diagnosis. What is necessary is some assessment of seriousness or severity which leads to major or incapacitating consequences. What is necessary are more specific criteria. No doubt this will occur in the course of time.

DISCUSSION

We probably are entering a new era in the investigation of depressive illnesses. We are

beginning to develop some laboratory tests which are meaningful, as well as new possibilities for epidemiological evaluations. It seems reasonable that we might separate out an illness which would be similar to depression spectrum disease or reactive-neurotic depression which would manifest itself by the following criteria. The patients would have a series of major personal problems; they would be quite responsive to stress; they would be normal responders in the dexamethasone suppression test; and they would have a family history of alcoholism. The biggest problem here is to systematically define a neurotic or stormy life-style. This is something that ought to be able to be put in a systematic form though it will require effort. These patients should be compared to those patients with a lack of alcoholism in their family, a presence of familial depression, a lack of stormy problems in their

lives, and an abnormal dexamethasone suppression test. These criteria would take all of the material that shows an association between the old clinical dichotomy and the familial separation and put them together. It is quite conceivable that such a set of criteria would offer us some increased precision in diagnosis and ultimately also in treatment. It seems doubtful that a simple effort to separate the patients on the basis of their clinical picture is going to lead to anything very productive at the present time. The relative ratio data make the diagnosis based simply on clinical picture suspect. The clinical picture has been around a long time and has served its purpose, but now it is necessary to look at things which have not been exploited as much, namely the genetic or family background and a set of laboratory tests.

We wish to acknowledge Raven Press, New York, for George Winokur, “Controversies in Depression, or Do Clinicians

Know Something After All?," in P. J. Clayton and J. E. Barrett (Eds.) TREATMENT OF DEPRESSION: OLD CONTROVERSIES AND NEW APPROACHES.

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OPEN DISCUSSION

Dr. Hagop Akiskal: I found Dr. Winokur's reformulation of the clinical and research controversies in the classification of depressive disorders to be both interesting and challenging. I would like to suggest several modifications with respect to the question of the "stormy life-style" that occurs in the context of affective syndromes. First of

all, this can occur as a result of cyclothymic and bipolar II disorders. It can also occur in some patients with high frequency episodic depressions. The remissions are so short and the interpersonal consequences of the illness so prominent that these conditions are often confused with a chronic personality disorder. As shown by our group *(Am. J. Psychiatry* 134:1227, 1977; *Arch. Gen. Psychiatry 37:171,* 1980), in all of these recurrent subaffective and affective disorders the affective condition is concealed by the stormy life-style. Thus, characterologic disturbance can "mask" affective symptoms very much like somatic complaints masking underlying depression. Indeed, we have shown that a substantial proportion of patients labeled "neurotic" or "characterologic" depressions do progress upon prospective follow-up into full-blown melancholia. The biological markers described are of great help in diagnosing these masked melancholic, or subaffective, illnesses.

My second point is that there exists another group of individuals with stormy life-style and depression whose primary pathology is characterologic. Even in your own studies the "depression" of this group has been shown to

occur in the setting of pre-existing and lifelong characterologic disturbance, as well as family history of alcoholism rather than affective illness. It would seem to me that the designation of "character spectrum disorder" or "characterologic dysphoria"—as proposed by us—is terminologically more descriptive than "depression spectrum," the term preferred by your group.

Dr. George Winokur: I was reading Dr. Akiskal's paper on the train down from Providence to New York, and I think he showed very well that the group of "neurotic-reactive" patients is a mixed group. I would have no problem at all with the way he suggested separating them. The thing that particularly intrigued me in his paper is that a large number of patients who meet that sort of clinical picture are secondary depressives as well. This is a problem, and the group does have to be divided.

Dr. John Rice: Care must be taken when interpreting a ratio of the rate in relatives of affected individuals to the population base rate. There is a measurement, the K-ratio, proposed in the genetics literature by Penrose in the early 1950s. This K-ratio now appears to have

limited utility in quantifying familial resemblance. More importantly, the magnitude of the K-ratio depends on how rare the disease is. If the prevalence of a disease is 25%, the largest the K-ratio can be is 4 (with all relatives affected), whereas if the prevalence was 1%, the K-ratio would be, say, 10 if 10% of the relatives were affected. Accordingly, it is not clear if higher K-ratios with severe (i.e., rare) illness can be interpreted as a higher degree of family resemblance.

Dr. Winokur: How would you correct for that?

Dr. Rice: I prefer to think in the context of genetic models based on a continuous underlying liability scale with affected individual corresponding to individuals having values above a certain threshold value. The estimate of the underlying correlation is given by the tetrachoric correlation coefficient and would be invariant under different threshold points so that cutoffs corresponding to different population prevalences can be compared. Thus, comparison of tetrachoric r's could be used to disentangle the effects due to different degrees of family resemblance and due to different population rates.

Alternatively, the 2 x 2 table of disease state in an individual and dis ease state in a relative could be analyzed using, say, an odds ratio. However, this approach might require the rates of illness in the relatives of unaffected individuals. Also, the 2 x 3 table of mild/severe illness in the proband, and unaffected/mild/or severe illness in the relative might be interesting to look at.

Dr. Barney Carroll: George, I really want to thank you for putting the searchlight on this whole issue of criteria in relation to diagnosis. If I can summarize what I think you have said, it is that criteria are necessary for diagnosis of depression, but that they are probably not sufficient in and of themselves and that some other discriminative ingredient goes into declaring an individual as a case rather than a noncase, and that this is a discriminative judgment that goes beyond the simple application of criteria.

This is the problem we have always had attempting to explain to other people and to funding agencies the way we do things in our own unit where we say that the person must meet criteria for endogenous depression, but in addition the clinicians have to agree that

this is a genuine case. I think these figures really support the way we have been going about it.

The other comment I would like to make is a further extension of what you said about individuals identified in the population simply by criteria. I think it is a very important one for people engaged in research. In some centers, subjects for research studies are recruited by newspaper advertisements; they are, in effect, symptomatic volunteers who are then entered into research studies. I have always had a great deal of skepticism about the validity of that procedure. I think you just contaminate your research groups with subjects who are not real cases in the sense in which the community or a psychiatrist would identify them, despite the fact that they meet criteria. So, I think that your data today can serve as a very serious warning against contaminating research studies with symptomatic volunteer subjects.

Dr. Lothar Kalinowsky: Just one brief question. How would you classify those cases which Sargant described as atypical depressions and which responded to MAO inhibitors better than to

tricyclics and to ECT?

Dr. Winokur: How would I describe them? Well, that would depend on which definition I used. We are going to have a series of papers on atypical depression here. If you say that these are patients with marked personal problems and a lot of anxiety symptoms and hysterical symptoms, I would diagnose them as primary affective disorder, unipolar if they meet the criteria, and not if they don't. Now, if they meet the criteria for anxiety neurosis, I would diagnose them as anxiety neurosis. I think one of the problems is that a lot of the patients who have been called atypical depressives, in fact, are secondaries, but I think we probably will hear a little bit more about that today in this meeting.

Dr. Hans Huessy: One of my associates, Dr. Stephen Cohen, recently did a study of adults meeting rigid criteria for the diagnosis of depression. He divided them into those who had a history with aggression in the past and those without aggression in the past. They were matched as to age and sex. What he found was that, of the people who had depression with a history of aggression, there was a total remission of symptoms in 7 days in 100% of the cases. In

the depressives without such a history, 0% showed that kind of remission. The two groups differed dramatically in their past histories, making one speculate that these two groups of patients are very different and that the aggressive depressives very likely are grown-up hyperkinetics. Often the response to medication is almost immediate and clearly involves a different biochemical effect than in the usual endogenous depression. The definition of reactive depression then would include a large number of grown-up hyperkinetics. Since childhood hyperkinetics do respond to small doses of tricyclics immediately, and we have also demonstrated that the same is true for grown-up hyperkinetics, I believe it is crucial that we separate this group of patients from our usual diagnostic category of depressive illness.

Dr. Frederic Quitkin: I want to support the suggestion that what is considered a neurotic depression is probably several different groups of depression. We have done two studies with two types of antidepressants in two separate samples of approximately 100 consecutive patients who had Hamilton depression scores of less than 18, and in both studies we

defined a group we called chronic dysphorics. It is a term proposed by Don Klein and essentially describes patients who say they are chronically unhappy. Temporarily they may have a better mood, but most of the time they are unhappy. In any event, we thought those patients would not respond to drug or placebo, and we were wrong. They have a higher placebo response rate than patients we call endogenous or endogenomorphic. But, more surprising, in both studies they have drug-placebo differences; with a big enough sample the drug-placebo difference probably would be statistically significant. About 50% of the patients responded to antidepressants as opposed to about 25 or 30% to placebo. This suggests to me that included there are at least two groups of patients—those who are responding to placebo, and those who have a specific drug effect. At present I do not know how to identify these groups prospectively.

Dr. Joseph Zurbin: I think this is the most thought provoking paper I have heard recently, and it really raises fundamental questions. I have only one particular point to raise: What is the implication of the fact that one group is an old, long ago group going back several

generations and the other is a current one?

Dr. Winokur: Actually, there is no marked difference in age. The groups are essentially controlled for age, and so are the family members, and there is not enough difference in mortality to account for differences. We are really studying proportionally the same groups from each epoch of time. That is not a problem. In other words, there were the same proportions of relatives of controls who were at risk for hospitalization in an Iowa state hospital as there were for relatives of depressives and manics.

Dr. Zubin: You had to treat them with reference to the customs and practices, the expectations and attitudes, of earlier epochs.

Dr. Winokur: It was certainly different in those days, but the thing is that both groups had equal numbers of people at risk in those days, both the control and the sick groups. We are dealing with groups of people who were living at the same time and were at risk for hospitalization. It is true that those who are alive at the present time are living in a different milieu, and should have a higher amount of illness. This should be true in both

the control relatives as well as the relatives of the manics and depressives. In fact, all do. The use of just the interviews makes them all higher than the records, but the relatives are controlled for age and time of ascertainment.

Dr. Craig Nelson: People have turned to other markers for classifying depression because use of symptoms alone has often been disappointing and it is sometimes difficult to agree on the symptoms that a presenting patient has.

It certainly makes sense to consider family history of illness, but isn't it even more difficult to agree on the symptoms or the classification of a family member who had an episode in the past? I thought your approach to this question suggests one alternative—that hospitalization may be a useful marker. I was curious about your experience with this question and whether you think there are other markers for classifying depression in family members.

Dr. Winokur: For practical purposes one of the things we do is diagnose a person as having affective disorder on the basis of a remitting illness. The individual has been well most of his life,

but had an illness during which he was incapacitated and then got well. That kind of data is possible to obtain from a family member because, interestingly enough, when you do a family history you get a follow-up on the family member. Most of the family members are not ill at the time of interview. So what you can get is reliable. We have tested that out; Bill Coryell and I have tested reliability by looking at the same family histories to see whether we agree on remitting illness versus chronic illness (which we thought was schizophrenia), and we were in good agreement. It depends to a large extent on a family member having a remitting illness from which he gets well ultimately. If at all possible we like to see somebody say that he was despondent or had depressive symptoms. But sometimes you have to just go on the remitting illness versus the chronic illness.