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ALCOHOLISM AND DEPRESSION: A REVIEW

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A REVIEW

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B.A. 1975, New College

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of the Requirement for the degree of
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1980

It is not for Kings, O Cemuel, it is not for
Kings to drink wine; nor for princes strong drink:
Lest they drink and forget the law, and pervert
the judgement of any of the afflicted.
Give strong drink unto him that is ready to
perish, and wine unto those that be of heavy hearts.
Let him drink, and forget his poverty, and
remember his misery no more.
Ecclesisates 31:4

It is not for Kings, O Lemuel, it is not for
Kings to drink wine; nor for princes strong drink:
Lest they drink and forget the law, and pervert
the judgment of any of the afflicted.
Give strong drink unto him that is ready to
perish, and wine unto those that be of heavy hearts.
Let him drink, and forget his poverty, and
remember his misery no more.
Ecclesiastes 31:4

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INTRODUCTION

Of the eighty to ninety million drinkers in the United States, about six million can be considered to be suffering from the disease of alcoholism (1). As in any addiction, these ill persons suffer from a more or less compelling psychic, emotional and/or physical dependence on alcohol. Drinking may be perceived as their chief source of pleasure or as a way of coping with the problems of everyday living--at work, or at home, or in other social situations. There is mounting evidence now that many alcoholics drink to overcome depression, and that depressed alcoholics drink more and have greater alcoholic morbidity than non-depressed alcoholics. The nature and therapy of this depressed mood has recently received increased attention. Researchers have tried to determine the relationship between depression and alcoholism--to determine if the depression is primary or secondary to the alcoholism, whether endogenous or a reaction to the many losses experienced in the life of an alcoholic. Until recently, researchers have failed to consider the role of depression in limiting the success of alcoholism treatment programs.

Much evidence suggests that the relationship between alcoholism and depression may be genetic. When a genetic basis to an illness is postulated, a significant biochemical component in the etiology of the disease is implicit. Thus genetic, constitutional, and other similarities found between alcoholism and depression might be related to common

etiological mechanisms. Furthermore, alcoholism may secondarily produce biochemical changes which are similar to those hypothesized to be responsible for affective disorder, or which are instrumental in lowering an individual's threshhold to this group of illnesses. If the biochemistry of these two disorders were similar, then it would also be reasonable to test with alcoholics medications known to be effective in affective disorders.

The literature of these various areas will be explored and reviewed in this paper, beginning first with early theories on alcoholism and depression, data on the characteristics of depressed alcoholics, and studies on the prevalence of the problem of depression in alcoholism. Evidence will be presented for a genetic relationship between the two disorders, as well as for various subgroups of depressive illness associated with alcoholism and various subgroups of alcoholism associated with depressive illness. Thereafter, the pharmacological effects of alcohol on mood will be explored as well as possible biochemical relationships between alcoholism and depression. Finally, attempts to treat alcoholism with antidepressant medications will be reviewed.

ALCOHOLISM AND DEPRESSION--
THE PROBLEM

DEPRESSION: A CAUSE OF ALCOHOLIC MORBIDITY

Historically many authors have considered depression as a cause of alcoholism. Rado (2), in 1932, described "pharmacothymia" as an illness characterized by a craving for drugs, including alcohol, to allay and prevent pain. He described these individuals as having a "tense depression" which he believed initially sensitizes the patients for the pharmacogenic pleasure effect of the drug (alcohol) to which they become addicted. And he added that "many drugs, especially alcohol, admit of combating the recurrent depression (of the patients) by overlapping dosage. The patient takes a fresh dose before the effect of the previous one has ceased." Amark (3), in his study on alcoholism in 1951, described the "urge to drink" among alcoholics to be "preceded by a number of physical symptoms or it arises as a consequence of some depressing psychic affect," and in discussing "periodic drinkers" he mentions that a depression secondary to situational life events and conflicts is closely connected with and seems to precede a drinking period. He also noted that personality types with a disposition for states of depression such as "cycloid persons" are more numerously represented among alcoholics and use intoxication with alcohol to quickly overcome their low moods. Kraeplin (4) in discussing dypsomania, "a periodical instinctive setting in of the tendency to drink, while in the intervals little or nothing is usually taken," states that the starting point of every

attack "is a state of depression, a feeling of discomfort and restlessness within, which patients try to escape by drinking."

Some studies, in fact, have shown as association between depressive feelings and craving for alcohol and/or relapse (5,6,7,8,9,10,11). Mathew *et al* (5) found the mean profile of Mood States depression score for their severe cravers to be more than one standard deviation above the expected mean, and, eighty-five per cent of their subjects related craving to unpleasant environmental factors, while eighteen per cent to endogenous depression. Ludwig (6) discovered only one per cent of the patients in his study offered reasons akin to craving as an excuse for "falling off the wagon," while the largest proportion of patients (forty-three per cent) cited some type of emotional dysphoria or unpleasant situation as the major cause. A couple of studies (7,9) showed high correlations between anxiety/craving and depression/craving, but the sample sizes were too small to show any significant relationship between mood level and drinking behavior. Ludwig and Stark (10) demonstrated that craving occurs when an alcoholic is emotionally dysphoric or during stressful, unhappy situations, such as when he is feeling anxious, worried, depressed, lonesome, or bored. He regards craving as a label attached to most dysphoric emotional states in alcoholics which provides them with an

acceptable excuse to continue or resume drinking. Litman _et al_ (11) showed that relapse precipitants could be categorized as either an unpleasant affect such as anxiety or depression, external events and euphoric feelings, social anxiety, and lessened cognitive vigilance. He states that the alcoholics poor and ineffective repertoire of coping behaviors in such dangerous situations are important in bringing about the relapse.

Pitts and Winokur (12) state that many periodic drinkers are persons who have cyclic attacks of depression and whose bouts of intoxication clearly occur only after a period of low mood, anergia, loss of interest, weight loss, terminal insomnia and other depressive symptoms. They also state that it is common for depressed patients to take alcohol for daytime and nighttime sedation, but they develop such tolerance that they are soon using very large quantities and chronic alcoholism results. Rosenberg (13) in his study of young alcoholics found that a number of his patients with personality disorders complained of periods of depression which preceded the onset of their heavy drinking and that many used alcohol for the relief of symptoms of depression. Suwaki (14) described several case histories of alcoholics who drank heavily while in a depressive state or to release themselves from painful emotions arising from interpersonal relationships.

Other authors do not agree on the overriding importance of depression as a cause of alcoholism. Mayfield _et al_ (16)

found some degree of correlation between mood and drinking in only seven of twenty-one alcoholics with a history of depressive affective disorder. Several of these patients drank excessively with the onset of a well defined depressive episode. However, since two thirds of the depressive group did not have an association between depressive episodes and drinking, these authors conclude that the two are not as a rule related. Curlee (17) feels that chronic depression may be an extremely important part of the alcoholic's personality and that for some drinking may be a reaction to their depression in an attempt to "self-medicate." She examined patients entering an Alcoholic Treatment Unit with interviews and psychological testing, and found marked qualitative differences in depressive feelings and the manner patients coped with these feelings. A small group of patients had a generally sad manner and seemed never to have experienced joy. Another larger group of alcoholic patients had a chronic depression which was a basic part of their personalities and stemmed from feelings of oral deprivation and oral rage associated with an infantile personality and frustration over not having their insatiable demands met. She suggests that a major factor in the etiology of their alcoholism may have been their effort to escape depressive feelings that they never learned to tolerate. A third group of patients reflected a depressive-masochistic personality which can not tolerate success and, therefore, spoil it by drinking.

She states that in a minority of patients no obvious, severe character pathology could be found, and so, in these patients, depression was more clearly reactive to external situations. She feels that it is important in therapy not to view depression as an unimportant side issue (something that will correct itself when the patient is no longer drinking) but to deal with it and help the patient learn to tolerate the depression long enough to deal with it effectively and adaptively.

Emphasizing that group of alcoholics which Curlee (17) considered to be trying to escape depressive feelings, Fox (1) used a new classification of depressions by Blinder (18) to describe the relationship of depression to alcoholism. The first classification, of physiologic retarded depression involves patients who usually give up alcohol as it merely worsens their condition. The second classification, of tension depression, also called reactive depression, is a state of continuous unresolved anxiety and nervousness. This type of depressed patient is very prone to turn to alcohol to allay symptoms which can readily lead to a dependence. Schizoaffective depression, the third classification, includes patients who frequently resort to alcohol to assuage their loneliness, their emptiness, and their depression. The fourth classification, of depression secondary to a problem in living, involves persons who are ill equipped to deal with the usual reverses of normal adult life and who often turn to alcohol and may become dependent on it. This is

in spite of the fact that depression may be appropriate for the situation. The final classification, of depression as a symptom of organic illness, also includes persons who may use alcohol to overcome their depressive state.

Other authors believe that a cause and effect phenomenon can not be established, since depression and alcoholism are nearly inseparable. Gibson and Becker (19) studied a group of jailed male alcoholics who had not sought voluntary treatment, in an effort to determine the extent of similarity between the factor structure of alcoholic depression and that of primary depression. Using the Beck Scale and the Zung Scale, major similarities between the affect described by alcoholics and that of primarily depressed patients were demonstrated. Self-debasement (self-dislike, guilt, failure), Vital Depression (fatigability, loss of libido, insomnia), and Pessimism-Suicide, a mood component, seemed to be as valid of characteristics of depression within a sample of alcoholics as they have been in primary depressives. This is despite the fact that the absolute levels of depression were significantly different with alcoholics showing a Zung depression score of forty-eight above the normal score of thirty-three, but below that of depressed controls (outpatients sixty-four; inpatients seventy-four). Functional Impairment, however, did not appear as important as the other three factors in the alcoholics as in the depressed patients. Gibson and Becker feel that this factor discriminates endogenous from reactive

depression and further suggest that there are few, if any, endogenously depressed alcoholics, with the lower depression scores of the alcoholics largely a function of quantitative differences. Overall _et al_ (20), however, believe that alcoholism and endogenous depression may be very closely related on the basis of alcoholic's favorable response to lithium and tricyclics.

Pottenger _et al_ (21) also noted that for descriptive symptoms of depression, the patterns shown by alcoholics were similar to those of primary depressives with the depressive symptoms of alcoholics in their study including disturbances of mood, sleep, appetite, and sexual functioning--accompanied by anxiety and suicidal feelings. Shaw _et al_ (22) compared the personality characteristics of alcoholics and depressed patients, finding alcoholics to resemble recovered depressives in lacking energy, bound to routine, cautious, and tense. Alcoholics differed from depressives in being more emotionally unstable and more vulnerable to stress. In comparing emotional states and behavioral patterns in alcoholics and non-alcoholics, Tokar _et al_ (23) found both groups to have similar emotional states, but, the alcoholics differed in their behavioral responses. When alcoholics had feelings of dependency, depression, anger, or anxiety, they saw their bartender, drank booze, smoked, and took pills. Therefore, alcoholics failed to utilize constructive outlets when they were depressed and, instead, used alcohol as a way of handling

problems that should be handled in other ways.

Whether or not causal, depression increases the severity of alcoholism. Using the Minnesota Multiphasic Personality Inventory, the group average MMPI profile of alcoholics has most frequently shown the highest scores on scales D (Depression) and Pd (Psychopathic deviate) (24-28). Whitelock et al (25) compared the degree of self-report of alcohol abuse among one hundred thirty-six newly admitted male patients in a state psychiatric hospital. He found the four predominant MMPI profile patterns to be one with elevation of Pd, one with elevation of D, and two with elevations of Pd, D, and Pt (Psychasthenia). The group having the prominent Pd score was low in self-report of alcohol abuse, while those with the highest levels of alcohol abuse had pattern profiles that pointed toward subjective discomfort and depression as the predominant factors. They concluded that it is anxiety and depression, and not hostility nor deficiency in impulse control that characterize the severe alcohol abusing patient. Fine and Steer (29) have also found a link between the degree of affective disturbance and the severity of alcohol dependency. They showed that consumption of alcohol to intoxication level and more frequent drinking behavior were associated, very clearly, with the more profound depressive states; and that patients in these states were also more likely to complain of drinking upon awakening. This may be related to alcohol withdrawal symptoms, but could be seen as a response to

waking early and feeling particularly depressed as is characteristic of moderate to severe depression.

With treatment, regardless of type, alcoholics had a significant improvement in MMPI depression scores in many studies (26, 27), and as again documented by Gibson and Becker (30), depression has a precipitous drop during the early stages of inpatient treatment of alcoholism. Still, depression has a significant impact on the the treatment success of alcoholism itself. Castor _et_ _al_ (31) using the Beck Depression Inventory, Lexington Addiction Research Scale for Psychopathology, and the Levenson Tridimensional Locus of Control Scale, found that depression scores increased systematically and significantly with decreasing success in treatment among alcoholics. Castor also found that there was a significant relationship between depression and feelings of control by others more powerful, however, these patients were less depressed and more successful in treatment than the patients who were depressed but did not relate their depression to feelings of control by others. Pottenger _et_ _al_ (21) also demonstrated a positive association between severity of impairment due to alcoholism with the presence of depression and treatment failure.

PREVALENCE

Many investigators have attempted to determine the prevalence of depression in the alcoholic population. Cadoret and Winokur (32) discovered that a large proportion of primary alcoholics had a depressive syndrome by psychiatric diagnosis at the time of hospital admission. This is similar to a recent study by Zielinski (33) in which forty-two per cent of the men and fifty per cent of the women were clinically depressed at the time of their first admission to a private treatment facility for alcoholism. Clinical depression was defined as a t-score of seventy or above on the D scale of the MMPI, eighteen or above on the Beck Depression Inventory, and fifty or above on the Zung Self-Rating Depression Scale (34, 35). He found women to be significantly more depressed than men, and he found these first time admissions to be more depressed than the relapsed group who were older, had a longer drinking history, and were treatment failures. Using the Zung Self-Rating Depression Scale, Weingold _et_ _al_ (36) found seventy per cent of male admissions to a state hospital alcoholic treatment service to exhibit mild to deep depression, and Shaw _et_ _al_ (37), using as criteria elevation in the Zung Self-Rating Depression Scale, the Beck Inventory, or the depression scale of the MMPI, reported a prevalence of depression of ninety-eight per cent among patients requesting treatment at a halfway house.

A recent study by Pottenger _et_ _al_ (21) found that a majority (fifty-nine per cent) of sixty outpatients admitted

to a mental health center for the treatment of alcoholism were clinically depressed as determined by a Raskin Depression Scale score of seven or higher (38, 39, 40). Using the Hamilton Depression Scale (41), Symptom Checklist 90 (42, 43), and Center for Epidemiologic Studies Depression Scale (44), These depressed patients were judged both by the clinician and by themselves as significantly more symptomatic and more socially impaired, compared with the alcoholics who did not meet the three criteria of depression on the Raskin Depression Scale (verbal report, behavior, and secondary symptoms). At one year follow-up, the depressive symptoms noted at intake still persisted without any significant change. They also noted a significant relationship between being depressed at follow-up and continuing to drink, with thirteen of the eighteen patients (72%) who were depressed at follow-up still drinking, whereas, nine of the twelve patients (75%) who were not depressed were not drinking even though both groups had attended the standard treatment program for alcoholics.

A lesser prevalence of depression is noted when depression is measured after withdrawal. Using psychiatric assessment of data from structured interviews, Fowler <u>et al</u> (43) diagnosed five per cent of alcoholics admitted to a psychiatric inpatient unit as having secondary depression, and Suwaki (14) diagnosed nine per cent of male alcoholics admitted to the hospital as having affective disorder (five with primary affective disorder, four with depressive neurosis, and five with chronic depression and transient paranoid symptoms).

He excluded from his study alcoholics who showed transient depressive symptoms after detoxification. Kielholz (15) similarly diagnosed a depressive condition in only five per cent of alcoholics after completion of detoxification and resolution of the "withdrawal depression." Both Kielholz and Pitts and Winokur (12) report that a markedly depressive and morose mood usually lasting two to three weeks is typical for alcoholics during the withdrawal phase, and that this is often followed by an apathetic depressive condition which may continue for six weeks or longer. He stresses that it is only possible to make an accurate diagnosis of depression after this "withdrawal depression" has been resolved. In a study by Tyndel (46), over one thousand hospitalized alcoholic patients were interviewed after they had recovered from alcohol withdrawal and/or acute illness. Using psychiatric interview and appraisal to make a diagnosis, twenty-six per cent of the patients showed serious depressive symptoms either at the time of interview or in the past history.

Prevalences vary according to the objective or subjective criteria used. In a recent study by Keeler *et al* (47), a population of thirty-five recently detoxified alcoholics was given the Hamilton Depression Rating Scale, the Zung Self-Rating Scale, the MMPI, and a clinical diagnosis based on an interview. By clinical diagnosis, nine per cent were found to be depressed; using a cut-off score of twenty on the Hamilton Depression Rating Scale, twenty-eight per cent

were depressed; using a score of forty-four on the Zung Scale, sixty-six per cent of the patients were depressed, and on the MMPI forty-three per cent of the patients had scores exceeding seventy on the depression scale. These authors conclude that depression should not be diagnosed in alcoholics using rating scales alone, and emphasized that the scales used in the study were either not designed to diagnose depression or have not been verified clinically for that purpose.

Subjectivity is evident when measurements are based on alcoholics self-report. Some alcoholics are very defensive and use denial of unfavorable emotions to keep up a positive self image, and to cope with depression. Hoffman (28) found alcoholics to be dependent on the approval of others and thus denied unfavorable personality traits and negative emotions to achieve this. In a study by O'Leary _et al_ (48), alcoholics appeared to have a distorted perception of self and were unaware of the degree of their depressed states. These authors used the Beck Depression Inventory (BPI) as well as assessments made not only be the treatment staff but also by other alcoholic inpatients and the patient himself. A significant positive correlation was found between staff ratings and other alcoholic inpatient ratings of depression, while the patients themselves had a distorted perception of their own depressed state. The magnitude of this perceptual distortion was found to be positively related to the degree of depression, with the greatest discrepancy noted in the more

depressed patients who tended to rate themselves as less depressed than their BDI scores indicated. Thus, through the effective utilization of defense mechanisms, particularly denial, the alcoholics tended not to observe those cues necessary to judge accurately the degree of their own depression. In another study by Freed et al (49), alcoholics were assessed at three month follow-up from a VA Hospital Alcohol Rehabilitation Unit using the Profile of Mood States rating scale. They found that abstinent subjects had a very low degree of affective disturbance, while the unimproved subjects had the highest levels of depression, with the slightly improved patients intermediate between the two other groups. These authors suggest that the extremely low scores of the abstinent veterans on the depression scales were a denial of their psychopathology used as an important defense mechanism to stay sober.

Further, in reviewing any data involving prevalence of depression among alcoholics, selection bias must be considered. Some studies indicate that alcoholics seeking treatment have a greater tendency to have two serious disorders, for example, both alcoholism and depression, than those who do not seek treatment. Woodruff et al (50) found that patients who had sought treatment for alcoholism at a psychiatric clinic were similar to alcoholic relatives who had not sought treatment, except for the presence of depression. Depressive symptoms were present at the time of interview and were probably

important as immediate reasons for the alcoholics seeking psychiatric attention. Thus data collected on alcoholics seeking psychiatric attention may not be representative of alcoholics in the general population. Hamm _et al_ (51) performed quantitative measurements of depression in a group of forty-eight men referred for treatment solely on the basis of excessive drinking, and compared their results with study groups who sought treatment reported in the literature. They found the prevalence of depression in their patients to be lower than that found in previous studies. Their patients were also younger than those in most other studies and the authors hypothesized that their low incidence of depression could also be due to the fact that they had not suffered alcoholism long enough to result in major life losses, or to the fact that depression is more common in older people in general.

Widely varying prevalences, therefore, are reported of depression among alcoholics depending on the population studied, the time of study during the course of the illness, and the methods used to assess and diagnose depression.

ALCOHOLISM, DEPRESSION, AND HEREDITY

Goodwin (52) states that "for many centuries it has been known that alcoholism was familial. Aristotle declared that drunken women 'bring forth children like temselves.' Plutarch said, 'one drunkard begets another.'" Early work by Sherfy (53) and Beuler (54) demonstrated that alcoholism was a highly familial morbid condition. Amark (3) in his early investigation of male alcoholics reported that depressive syndromes were more often found in the relatives of alcoholics than in the general population, and that male first degree relatives had a higher incidence of alcoholism than would be predicted from the general population. The genetic basis of the familial incidence of alcoholism is now a relatively undisputed fact (52, 55-59). There is also little doubt as to the recognition of genetic influences in the development of, or predisposition to, affective disorders (60-63). Although environmental factors are very important in alcoholism, twin and adoption studies have shown that genetic factors also seem to be present (52, 55, 56). Another trend that has emerged shows higher rates of alcoholism in the families of female rather than male alcoholics (53, 55, 64). One recent study supports evidence for an X-linked recessive genetic characteristic in the inheritance of alcoholism (57). Studies show that almost one-third of any sample of alcoholics will have had at least one parent who was an alcoholic, and if one member of a family is an

alcoholic, eighty-two per cent of the time there is at at least one other alcoholic in the family (55). Alcoholism is also found to be more prevalent in male rather than in female relatives of alcoholics, and in near rather than in distant relatives (55, 64). Furthermore, in searching for mental illness in alcoholic's families only depressive and psychopathological features could be demonstrated in significant amounts (55).

Investigating affective disorder patients, Winokur and Pitts (65) discovered that these patient's parents had five times the prevalence of alcoholism as compared with controls. They also demonstrated that non-affective disorder patients admitted to a psychiatric hospital with a parental history of affective disorder to have a higher prevalence of alcoholism and personality disorders. In a later study, Pitts and Winokur (12) showed significant increases in affective disorder is siblings of alcoholic probands, and alcoholism was seen more frequently in first-degree relatives--mostly male--of affective disorder patients. Affective disorder was the only psychiatric illness, other than alcoholism, demonstrated in excess in near relatives of index case alcoholics, and has been shown to be two to four times as prevalent as that of the general population. Winokur and Clayton (16), in comparing male and female alcoholics found that more women had a secondary diagnosis of depression--including suicidal ideation-- and that there was more frequent diagnosis of psychiatric illness including depression and alcoholism in

parents of alcoholic women. Female alcoholics also had an increased incidence of affective disorder in their female siblings. Further considering the problem in a later study, Winokur et al (64) confirmed that alcoholism is much more frequently seen in male relatives (fifty per cent lifetime expectancy) of alcoholic probands, while affective disorders are more frequently seen in female relatives (fifty per cent lifetime expectancy) of the alcoholic probands. They also noted a significant increase in sociopaths of male relatives as compared to female relatives. They demonstrate that the affective disorder which is usually seen in alcoholics and their families is not manic-depressive disease. Finally, they hypothesize that the genetic propency to get alcoholism manifests differently in males and females--as if one adds the rates of alcoholism and affective disorder in all affected female relatives, this approximates the number of ill male relatives with alcoholism and sociopathy.

In summary, family histories of alcoholics indicate much higher rates of alcoholism than of any other form of mental illness. Higher rates of depressive and psychopathological features are reported in relatives of alcoholics than in relatives of controls; and relatives of patients having affective disorder, when compared with controls have higher rates of alcoholism and affective disorder.

PRIMARY AND SECONDARY DEPRESSION

Recently investigators have begun to classify depression as either primary or secondary. Winokur and Clayton (67) and Woodruff *et al* (68) define primary affective disorder as a current affective syndrome occuring in a patient whose previous history may be characterised as psychiatrically well, notable for a previous episode of depression or mania, or noteworthy for previous psychiatric symptoms none of which are inconsistent with the diagnosis of depression or mania. These symptoms may or may not have been episodic in the past. Secondary affective disorder is defined as a current affective syndrome occurring in a patient who has had a pre-existing, diagnosable, non-affective, psychiatric illness. The symptoms of the previous, non-affective psychiatric illness may or may not merge temporarily with those of the current depression. Woodruff *et al* (68) concluded that primary and secondary disorders can not be distinguished by their affective symptoms alone when the illnesses are severe enough to result in psychiatric hospitalization. He found the major difference between the two groups to be that the primary affective disorder patients regarded their illness as discrete, in that they felt distinctly different from usual, while the secondary affective disorder patients regarded their current affective symptoms as a worsening of their usual state, rather than as a new experience.

Guze *et al* (69) determined that the most common

psychiatric disorders associated with secondary affective disosders to be alcoholism, antisocial personality, anxiety neurosis, and hysteria. His prototype patient with secondary affective disorder was a young male not prone to mania. In contrast Winokur (70) found secondary depression more frequently in females. Winokur demonstrated that when depression is seen as a secondary disorder, it is most frequently secondary to alcoholism. Moreover, alcoholism was reported more frequently among the first-degree relatives of secondary affective disorder cases than among those of primary affective disorder cases. In studying characteristics of patients (including demographic, behavioral, family, and social variables) Woodruff et al (71) demonstrated that the patients with both alcoholism and secondary affective disorder to resemble most closly the patients with alcoholism alone rather than to resemble those patients with primary depression alone. This suggests that secondary depression may well be a result of the primary illness itself rather than consequent to other factors. This finding is in agreement with Cadoret and Winokur's conclusions (32), and, perhaps, indicates that secondary depression should be considered and studied separately from primary affective disorder, and in the context of the primary illness.

The frequency of secondary depression in alcoholics ranges from twenty-eight per cent to thirty-nine per cent, reported by Winokur (70), depending on the number of depressive symptoms required for diagnosis (four or three), to forty-one

per cent reported by Cadoret and Winokur (32), to fifty per cent reported by Guze _et al_ (69), to fifty-nine per cent reported by Pottenger _et al_ (21) as well as Weissman _et al_ (72). Several studies indicate that primary and secondary depressives have relatively similar symptom patterns but do differ in symptom severity (21, 32, 70, 72). The secondary depressives tend to report less severe depressive symptoms and to be rated as less symptomatic by the clinician (72). Cadoret and Winokur (32) in studying alcoholics demonstrated that in men with secondary depression, drinking tends to be more periodic and is more likely to be of the 'bender' type than in women. Furthermore, they showed that female alcoholics with either primary or secondary depression appear to have longer periods of abstinence than women with primary alcoholism. Thus, a strong relationship exists between secondary depression and alcoholism.

PRIMARY ALCOHOLISM VERSUS SECONDARY ALCOHOLISM

Several studies have compared patients with a history of primary alcoholism with patients with a history of secondary alcoholism and some other primary psychiatric disorder (73-76). The psychiatric disorders most commonly found to be primary when alcoholism was secondary were unipolar affective disorder and sociopathy. Males were found to predominate in two groups--that with primary alcoholism and that with primary sociopathy and secondary alcoholism; whereas, females predominated only in the group with primary depression and secondary alcoholism (75). Of two hundred thirty-nine consecutive female admissions to a public detoxification center, Schuckit and Morrissey (74), however, regarded fifty per cent to have primary alcoholism, fourteen per cent to have primary affective disorder and secondary alcoholism, and fourteen per cent to have primary antisocial personality with secondary alcoholism. On comparing female primary alcoholics with female affective disorder alcoholics, the latter are younger, from a higher socioeconomic strata, more isolated, less likely to have problems from drinking in public places, more likely to have attempted suicide, and more likely to have a family history of affective disease (73-75).

Schuckit _et al_ (73) demonstrated that rates of alcoholism and affective disorder were similar in the relatives of both groups of women. Whereas male relatives of both groups tended to be alcoholics, female relatives tended to have the same primary disease as the patient--alcoholism in the case of

first degree female relatives of primary alcoholics, and affective disorder in female relatives of alcoholics whose primary illness was affective disorder. When alcoholics of both sexes were categorized as primary alcoholics, depressed alcoholics, or sociopathic alcoholics--their family histories reflected these groupings (75, 76). Alcoholism was seen more frequently in first-degree relatives of the first group, depression in relatives of the second group, and sociopathy in relatives of the third. The risks for depression for all first degree relatives in these three groups were fifteen per cent, twenty-seven per cent, and nineteen per cent, respectively. Overall, in first degree relatives of alcoholics from all groups, alcoholism occurs more frequently in male relatives and depression in female relatives (75, 76). This is consistent with the hypothesis of depression spectrum illness discussed in the next section.

DEPRESSION SPECTRUM DISEASE

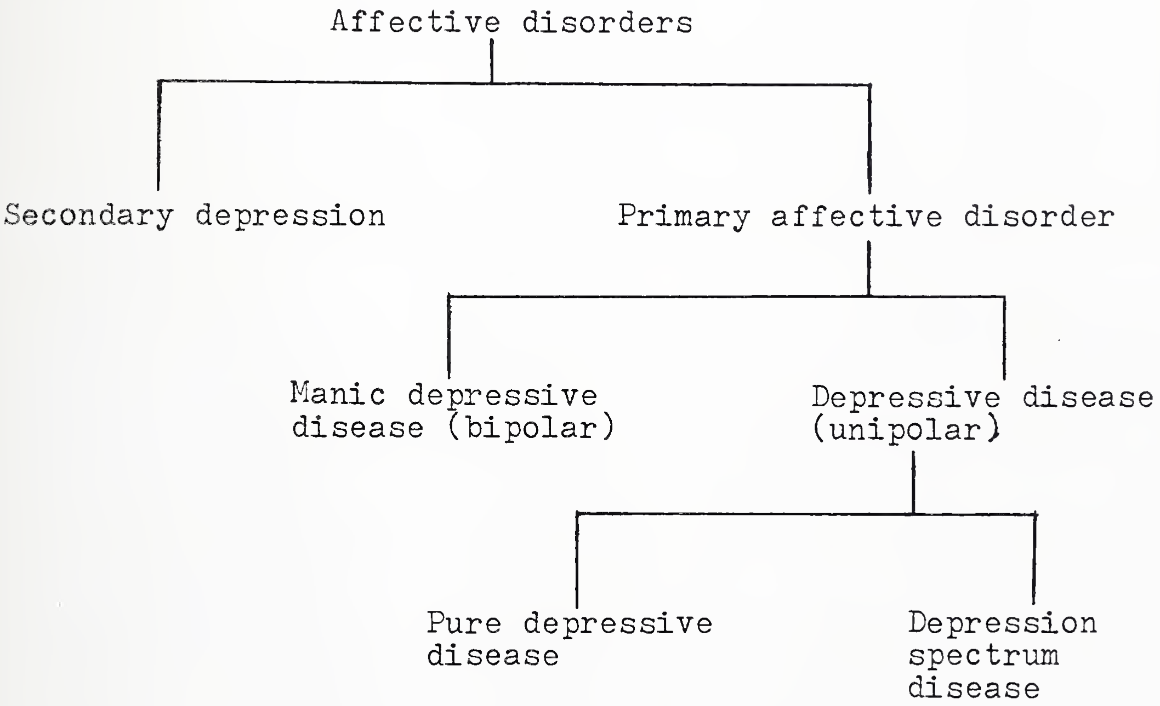
Many studies have suggested separation of two distinct, homogeneous groups of unipolar depressive illness differentiated by contrasting familial illness patterns. These are termed "depression spectrum disease" and "pure depressive disease" (77-83). Depression spectrum disease as compared with pure depressive disease has the following characteristics--relatively early onset (typically before age forty), a greater likelihood of familial affective disorder, significantly more female than male first degree relatives with affective disorder, a significantly greater prevalence of familial alcoholism and antisocial personality, and finally, a significant increase in total psychiatric illness (including depression, alcoholism, and antisocial personality). On the contrary, in pure depressive disease the onset is relatively late, the incidence of affective disorder is similar in male and female first degree relatives, there is only a negligible amount of familial alcoholism and antisocial personality, and there is less total familial psychiatric illness. Moreover, there is a striking association between the age of onset of depression in probands and that age in ill relatives.

This classification is derived from data which showed that parents and siblings were more likely to be psychiatrically ill in the early onset group. Also shown was a skewed distribution of depression in the early onset group with the female relatives much more likely to be depressed than male relatives. This skewed ratio was not demonstrated in the

late onset group nor in the group where the proband was male. The early onset group had a high frequency of alcoholism or antisocial personality among male relatives, and, furthermore, the large number of these illnesses was sufficient to compensate for the relative lack of depression in fathers and brothers. Thus, when alcoholism, antisocial personality, and depression were combined into one depression spectrum--there was an almost even distribution of illness between male and female primary relatives of early onset probands. When they considered alcoholic probands, the modal illness among male relatives was alcoholism whereas among female relatives, depression. They then concluded that it is possible that depression spectrum disease manifests differently in men and women--namely, as alcoholism and/or antisocial personality in men, but as depression in women. Thus, early onset unipolar affective illness differs from late onset unipolar illness which manifests as depression in both sexes (84).

Comparing depression spectrum females with pure depression females, Van Valkenburg _et_ _al_ (82), found few differences in their presenting picture. But, they did show some differences in the areas of personal problems, personality, and course of illness. Depression spectrum patients were significantly less likely to have loss of interest in usual activities, but they were significantly more likely to have had a history of sexual problems, to have been

divorced or separated, to be described as irritable, and to report previous depression. Furthermore, they were significantly more likely to recover completely without relapse. Thus these authors calssify affective illness as diagrammed below.



Cadoret _et_ _al_ (84) have obtained data consistent with a multigenic model of inheritance for depression spectrum disease, and unipolar affective disorder. But linkage studies (85, 86) have shown an internal consistency suggesting genetic homogeneity of depression spectrum disease, compatible with the hypothesis of the existence of such a disease. This also adds strength to the concept that alcoholism and depression existing in the same family are

manifestations of essentially the same illness--the difference in manifestation being an expression of phenotype between males and females.

BIPOLAR ILLNESS AND ALCOHOLISM

The acute alcoholic episode, with its initial elation followed by the depression of the withdrawal phase, may be considered a manic-depressive attack in abbreviated and miniature form. Historically the two were conceptually linked in the illness known as dipsomania, where pathologic drinking was considered to be symptomatic of manic-depressive illness (4). Early work by Cassidy _et al_ (87) found eight per cent of manic-depressives to be also chronic alcoholics. He noted that twenty-eitht per cent of patients with manic-depressive disease drank more alcohol when ill, while thirty-one per cent decreased their drinking. However, he did not differentiate between unipolar and bipolar patients or even between the manic or the depressive phase. Other studies have indicated the incidence of alcoholism in manic-depressive patients to range from zero to thirty-three per cent (88, 89) (zero to six per cent among non-hospitalized patients, and one to thirty-three per cent among hospitalized patients). Certainly the lower estimates are not very different from the incidence of alcoholism in the general population which is about five per cent.

Excessive alcohol use in manic-depressive illness appears to occur only in the manic phase; while in the depressive phase, patients tend to shun alcohol (14, 16, 88, 90-92). Only a few investigators have found patients to increase their consumption of alcohol in the depressive phase (88, 29). Therefore, in bipolar illness, drinking

seems to be positively and consistently related to elation and negatively related to depression. This is, of course, in contrast to alcoholics with depression but without mania who tend to drink heavily when they feel depressed. Reich _et al_ (90), in comparing manic-depressives who had never been hospitalized with hospitalized manic-depressives, found that only the excessive use of alcohol distinguished those manic patients with a history of hospitalization. Perhaps, this could explain the discrepancy in incidence of alcoholism among various studies as already noted. The patients themselves frequently reported the deliberate use of alcohol to attempt to calm themselves and to decrease manic symptoms.

Recent studies have indicated though that there is no causal relationship between alcoholism and manic-depressive illness, both of which might be considered as "primary" in an individual patient (93,94,95). Morrison (94) demonstrated that the rate of alcoholism in the manic-depressive population did not significantly exceed that for the entire psychiatric service. Morrison (93), in another study, investigating family histories of bipolar affective disorder patients with and without alcoholism, showed that affective disorder was seen in equal frequency in both populations, but that alcoholism was significantly more prevalent only in relatives of the alcoholic probands. This is in agreement with Dunner _et al_ (93) and suggests that bipolar affective disorder and alcoholism are most likely to be genetically transmitted independently.

Winokur *et al* (64) also demonstrated that the presence of mania in alcoholics and their families is simply a chance phenomenon. Thus, there does not appear to be an association between alcoholism and bipolar affective disorder.

SUICIDE

Alcoholism and depression share a common cause of death--suicide. Rado (2) believed that suicide was one of the ways alcoholics escaped a depressive crisis. Benensohn and Resnik (96) state that both alcoholism and suicide are often attempts to deal with intense intrapsychic pain. At present, suicide is the eleventh leading cause of death in the United States, and studies show that the life risk for suicide among both alcoholics and depressives to be about fifteen per cent (97, 98, 99), with a range of seven per cent to fifty-six per cent among alcoholics (98, 100-104)--while four to five per cent of the general population is alcoholic. Considering suicides as a group, Barraclough _et al_ (105) found that eighty-five per cent suffered depression or alcoholism with fifteen per cent suffering from alcoholism alone; and Robins _et al_ (106) demonstrated that approximately seventy per cent of deaths by suicide involved individuals with alcoholism or affective disorder. Some investigators feel that alcoholism is a kind of chronic suicide, wherein individuals seek a slow kind of self-destruction (102, 103).

Investigators have found that most alcoholics, as well as depressives, communicate their suicidal ideas repeatedly to a number of persons in the few months preceding their deaths (97, 105, 106). They have also found that approximately forty per cent had had medical care for their alcoholism in the preceding year, twenty-two per cent within one month, and

that eleven per cent had been examined by a psychiatrist within a year (106).

Investigators have also found that the risk for suicide among alcoholics increases with increasing age, with a median age of fifty-one years; moreover, the risk also increases with increasing duration of the disease, with a median duration of twenty years (98, 105, 106). Thus, the longer the alcoholism persists the more likely it is to cause adverse personal, social, and health changes which may increase the risk of suicide. However, one study found that younger suicides tended to be alcoholic, while older suicides were not (103). Studies have also found that among alcoholics, whites have higher rates of suicide than blacks, and men higher rates than women (103, 104).

Many studies have confirmed that alcoholics commit suicide as a result of actual or impending loss of status, occupational role, or interpersonal relationships (97, 100, 102-105, 107). Murphy and Robins (107) observed that alcoholics had commonly experienced or anticipated a major loss of a close affectional relationship within the last six weeks of their lives, suggesting that these events were important in triggering the suicide. Dorpat _et al_ (102) found that symptoms of depression could be elicited in every completed suicide and serious suicide attempt when adequate information was available. Barraclough _et al_ (105) and Schmidt (100) also recorded many depressive symptoms among

alcoholic suicides. Barraclough _et al_ found that the relative incidence of depressive symptoms was similar to that of the uncomplicated depressive suicides with the onset of the depression recent. Thus, the distinguishing characteristics of an alcoholic suicide were a combination of severe alcohol addiction and depression occuring in a recently disturbed domestic and social setting. Barraclough _et al_ (105) also noted that the past and family histories of mood disorder in the alcoholic suicides resembled those of the depressives.

Some studies have found that heavy drinking or intoxication is frequently present at the time of suicide, with about thirty per cent of those completing suicide drinking at the time of the act (96, 102). It could be that with prolonged drinking and intoxication, alcoholics may become depressed to suicidal proportions (89, 96, 99, 108). In this case, the depression can clear after a couple of weeks of abstinence, at which point the patients may wonder why they had attempted to kill themselves (99).

It has also been found that a high percentage, at least fifty per cent, of suicide attempters drink at the time of the suicide act. Rates of alcoholism among attempters ranges from thirteen to fifty per cent (103). As stated above, suicides are predominantly male and over forty, while suicide attempters are predominantly female and under thirty (97, 102, 103, 108). Cadoret and Winokur (32) found that in their population of depressed alcoholics, twenty-seven

per cent of them had made two or more suicide attempts in contrast to only five per cent of the non-depressed alcoholics. These findings have potential importance in the practical clinical management of alcoholic patients as multiple attempters are at higher risk for both further suicide attempts and completed suicides. There is a trend for the attempts in alcoholic men with depressive syndrome to be more serious (32, 29). Mayfield and Montgomery (108) found that of thirty-four patients admitted to the hospital from suicide attempts, twenty-nine were alcoholics, and, of these, twenty-six were intoxicated at the time of the attempt. Seventy-seven per cent of their patients had depression in mood prior to the suicide attempt. These authors have hypothesized that there are two types of suicide attempts which alcoholics appear to make. The first type has been described as "abreactive" and is characterized by sudden unpredictable attempts which occur at the onset of drinking or at a time of rapidly increasing levels of intoxication. The second type has been described as resulting from a "depressive syndrome of chronic intoxication."

Thus, alcoholics who are most prone to suicide are depressed, in the later chronic stages of their disease, have recently undergone a crisis or a major loss in a close affectional relationship, have recently and repeatedly conveyed their suicidal thoughts to others, and are intoxicated at the time.

EFFECT OF ALCOHOL ON MOOD

The high concordance between alcohol intoxication and suicidal behavior can be understood if intoxication is associated with the development of an increasingly depressed mood. However, many psychological theories of alcoholism have been based on the premise that intoxication favorably alters affect and alleviates emotional discomfort. Recent research, though, has shown that alcohol is, indeed, capable of producing profound sadness in both alcoholics and non-alcoholics. The intensity of this phenomenon depends on the original mood, the circumstances of drinking, and the amount of alcohol consumed (99).

Some studies have shown that intravenous infusion of alcohol has different effects on alcoholics and nonalcoholics (88, 109, 110). Using the Clyde Mood Scale, Mayfield and Allen (110) have shown that nonalcoholic depressed patients improve dramatically with intoxication, nonalcoholic controls show less but still definite improvement, and the alcoholic patients improved the least and actually showed a trend toward deterioration. In a subsequent study, depressed patients with a history of excessive drinking showed significantly less improvement in affect with intoxication than depressed patients who had never used alcohol excessively (109). Thus, these investigators found that one of the pharmacological effects of alcohol is the capacity to alter affect, especially when the affect is disordered, indicating a paliative

rather than a euphoriant effect. Mayfield (111) gave a drinking behavior questionaire to a group of sober alcoholics and found that alcoholics uniformly described intoxication as improving their mood and "picking up their spirits." He then infused alcohol intravenously and described at levels of mild intoxication, no change in affect--but, at higher levels of intoxication, a deterioration in affect, in direct contrast to the alcoholics expectations. Several other studies have noted a discrepancy in the way alcoholics feel during intoxication and how they think they will feel when asked prior to drinking (112, 113, 114). Tamerin et al (112) discovered that alcoholics, participating in a study in which they could drink up to one quart of bourbon daily for a fourteen to sixty day period, indicated that they drank in order to feel better and to become more sociable. However, the results showed that during late intoxication, the alcoholics regarded themselves as significantly more dysphoric. Vannicelli (113) also demonstrated that alcoholics tended to describe their intoxicated states as an improvement in affect, but, in fact, depression tended to increase with increasing doses of alcohol and progressive intoxication. Thus, these results indicate that alcoholics know very little about their drunken selves, and sober retrospective self-report about what they are like when drunk correlates poorly with the picture that emerges when intoxicated. Many of the early studies suggesting that alcoholics drink in order to improve

their mood and "to feel better" were derived from such sober self-reports. Other studies have also shown that when alcoholics drink they experience progressive increase in anxiety and depression with increasing doses of alcohol rather than a decrease (114-116).

Warren et-al (117) measured mood changes in twelve nonalcoholic college students at different blood alcohol concentrations and under three different conditions--intravenous injections, social drinking, and isolated drinking. As their blood alcohol concentrations increased, all the subjects tended to become significantly more depressed without any significant differences among the three groups. However, Williams (118), on studying the drinking of normals in a natural setting found that anxiety and depression decreased significantly at low levels of alcohol consumption, but, at high levels, anxiety and depression increased. This is in agreement with other studies on normals (88). Alterman et al (115) found this also to be the case among alcoholics. He demonstrated that drinkers experienced less discomfort during the first week of drinking and more discomfort during the following three weeks of drinking. However, he felt this was not due to the pharmacological effects of alcohol, but, rather, to the drinker's decision to drink instead of abstaining.

It is puzzling that alcoholics continue to drink despite the adverse effects of alcohol on mood that occur

during intoxication. It is possible that the transient mood elevation at the beginning of intoxication may be important for alcohol abuse, but this has not been determined. Mendelson and Mello (59), considering recent animal models in which aversive stimuli control behavior and are self-administered, suggest that it is possible that the dysphoric effects of intoxication are important in reinforcing drinking.

ALCOHOLISM AND BRAIN BIOCHEMISTRY

THE AMINE HYPOTHESIS AND AMINE CHANGES IN ALCOHOLISM

A large body of evidence from animal and human studies implicates the biogenic amines as important central nervous system neurotransmitters, particulary in those areas of the brain subserving "emotional" functions. Research on depression has produced the well known "amine hypothesis" which suggests that there may be a functional deficit of one of the catecholamine neurotransmitters--norepinephrine, dopamine, or serotonin--at the neuronal synaptic cleft in the central nervous system of individuals experiencing severe depression--with a functional increase in mania (119-128). More recent work has suggested that depression may be a biochemically heterogeneous disorder. Two subtypes have been hypothesized. The first, "norepinephrine depression," is characterized by low urinary 3-methoxy-4-hydroxyphenylglycol (MHPG) levels and successful treatment with desipramine or imipramine, indicating a possible deficiency of norepinephrine in the central nervous system. The other "serotonin depression," is characterized by normal or elevated urniary MHPG levels, low cerebrospinal fluid 5-hydroxyindolacetic acid (5-HIAA) (an end product of serotonin metabolism) levels, and successful treatment with amitriptyline indicating a presumed central nervous system (CNS) serotonin deficiency (122-125). MHPG is the metabolized end product of norepinephrine in the brain and the bulk of urinary MHPG is considered to originate from the cerebrospinal fluid (CSF), although the exact percentage

is not known (119, 122, 123, 129, 130). Laboratory studies have demonstrated that desipramine selectively inhibits reuptake of norepinephrine with little effect on serotonin, whereas, amitriptyline selectively inhibits the reuptake of serotonin with relatively little effect on norepinephrine, and imipramine inhibits serotonin and norepinephrine equally, although at one half the activity of either amitriptyline or desipramine (125). A third possible subtype has recently been described--a "schizophrenia related depression" characterized by low MHPG excretion and high levels of platelet monoamine oxidase activity (123).

One of the early findings that led to the "amine hypothesis" was the observation that reserpine, which decreases functional brain catecholamines, was associated with severe depression in high doses (121). Reserpine has also been shown to have central cholinomimetic properties with the depressant effects of reserpine being remarkably similar to those of cholinesterase inhibitors. Furthermore, there is now data to suggest that an adrenergic-cholinergic balance may underlie the affective disorders, with depression being a disease of cholinergic dominance and mania being the converse (126, 131). Proponents of this theory suggest that tricyclic antidepressants act primarily by blocking central cholinergic activity. This biochemical research on depression has begun to provide the basis of later research on alcoholism.

There has been increasing research aimed at elucidating

the biochemical mechanisms involved in alcohol dependence, withdrawal, as well as, the acute state changes. Alterations in catecholamine function in the brain have been observed after acute and chronic treatment of alcohol. Some studies in animals have shown an increase in central catecholamines with alcohol administration (132, 133) and withdrawal (134), while others have noted no change or even a decrease (134). Griffiths et al (132) noted an initial significant reduction in brain monoamine concentrations which was short lived during chronic alcohol administration. Thereafter, he noted a slow rise in catecholamines continuing into the withdrawal phase transiently, and finally a subsequent decrease to control levels over the next ten hours of withdrawal. Strombom et al (133) noted that alcohol's behavioral stimulant action in mice can be largely suppressed by apomorphine or clonidine--drugs which in the small doses used probably inhibit central catecholamine neurons (in larger doses clonidine is an alpha-receptor activating agent). These investigators suggest that the behavioral stimulation by alcohol is dependent on central catecholamine neurons and possibly related to alcohol's stimulating effect on brain catecholamine metabolism. Clonidine was also noted to speed the recovery time of withdrawal symptoms by one day for patients in moderately severe alcohol withdrawal (135). The effects of clonidine were especially noticeable with respect to tremor, sweating, elevated systolic blood pressure, tension, anxiety, and

depression. Research has also shown alcohol to increase norepinephrine and epinephrine excretion peripherally, as well as to induce a shift in catecholamine metabolism peripherally from normally oxidative pathways to reductive pathways (136-140). Most likely, this is secondary to competitive inhibition of aldehyde dehydrogenase by acetaldehyde. The shift in metabolism has not been found in the brain, but peripherally causes decreased amounts of urinary vanyllmandelic acid (VMA) and increased urinary MHPG (136, 137). These changes have been considered to be associated with the enhancement of anxiety and dysphoric states that occur as a consequence of prolonged drinking (136). Gitlow _et al_ (141) has demonstrated that previous alcohol dependency results in long term and, perhaps, persistent modification of the pharmacological response to alcohol challenge, and, furthermore, these changes may involve central biogenic amine metabolism.

Investigators have demonstrated that after single dose alcohol treatment in nonalcoholic rats central norepinephrine turnover shows a biphasic response (136, 142, 143) as it initially is accelerated, with an increase or no change in dopamine turnover. Several hours later norepinephrine, dopamine, and serotonin turnover are all reduced. Yet, in alcohol dependent rats, whether intoxicated or undergoing withdrawal syndrome, the turnover of norepinephrine was consistently increased while that of dopamine was decreased. Hence, these authors suggest that severe alterations in

catecholamine function may extend to a time period when there is no alcohol left in the body to depress neuro-excitability, and that this may lead to some of the symptoms associated with the withdrawal syndrome (136, 142-144). Reis (145) has produced evidence which supports the view that states of behavioral excitement in the cat, similar in many of its manifestations to delerium tremens in humans, can be evoked by activation of central noradrenergic receptors. Some research has shown that chronic administration of alcohol increases the sensitivity of central dopamine receptors, but not central noradrenaline receptors (146). Thus, many researchers have demonstrated support for the hypothesis that central catecholamine mechanisms are affected, on at least a short term and possibly a long term basis, by chronic alcohol administration.

Alterations in central serotonin metabolism have also been implicated as being involved in the alcohol withdrawal reaction (147-150). Both increases and decreases of central serotonin content have been reported following acute and chronic administration of alcohol (151, 152). The majority of studies in animals report that acute and chronic alcohol administration increases serotonin turnover (151). Alcohol can also shift indoleamine catabolism in the periphery from the phsyiological oxidative to a reductive pathway (153). On studying peripheral indoleamine metabolism, Banki and Vojnik (153)discovered that when given intravenous alcohol,

alcoholics reacted by a reduction of 5-HIAA output in urine, while controls showed no change in 5-HIAA excretion but a marked fall of serum serotonin. These differential changes seem to support the hypothesis that indoleamine metabolism may remain permanently altered in chronic alcoholism. A recent preliminary study by Ballenger _et al_ (151) found the CSF 5-HIAA of alcoholics in the abstinence phase, twenty-eight to sixty days after their last drink, to be significantly lower than both a nonalcoholic comparison group and alcoholics in the immediate post-intoxication phase within one to two days after their last drink. There was no change in homovanillic acid (HVA) which is the cerebrospinal fluid metabolite of dopamine. These investigators suggest that this is consistent with the hypothesis that the pathophysiology of alcoholism may involved pre-existing low brain serotonin levels that are increased transiently by alcohol consumption, but, that brain serotonin levels gradually undergo increments of further depletion as a consequence of repeated drinking. Furthermore, they suggest that this alcohol produced depletion would aggravate the postulated pre-existing serotonin deficit, establishing a viscious cycle in which the alcoholic repeatedly seeks to pharmacologically modify a central indoleamine deficit. These findings are particulary interesting in the setting of the "serotonin depression" hypothesis mentioned earlier in which there is a presumed CNS serotonin deficiency which can be successfully treated with amitriptyline.

If such data are supported in future work, it might be hoped that research will be done to determine if amitriptyline will reverse alcoholics indoleamine depletion and, thus, help them to stay abstient. One group of researchers (154) has proposed the hypothesis that the acute effects of alcohol are similar to those of monoamine oxidase (MAO) inhibitors--increasing biogenic amines--whereas, the chronic effects are similar to those of reserpine--depleting biogenic amines.

OTHER NEUROTRANSMITTERS

Besides the amine hypotheses discussed, there have been further hypotheses and research attempting to explain the action of alcohol on the brain as mediated by false neurotransmitters called tetrahydroisoquinoline alkaloids at catecholaminenergic receptors (145, 155, 156). These compounds have been considered to be formed by condensation of dopamine and the acetaldehyde from alcohol metabolism. Although these compounds have been formed *in vitro*, this has not been demonstrated *in vivo* (155, 156). These compounds are considered to be important in the acute narcotic effect of alcohol, as well as in alcohol dependence and withdrawal. There is also some evidence to suggest that these compounds are a possible "link" to opiates (155). However, due to the paucity of evidence for any *in vivo* role, interest in this field is waning.

Gamma-amino-butyric acid (GABA), an inhibitory neurotransmitter, has also been studied during alcohol dependence and withdrawal. Reports, however, have been contradictory--some showing increases in brain content of GABA after acute and chronic administration of alcohol, while others, a decrease or no change (152, 157). There is no good evidence at this time which implicates a disturbance of the GABA system as having a causal role in the genesis or maintenance of alcoholism.

Acetylcholine has been shown to decrease or remain

unchanged in animal brains after chronic forced intake of alcohol (158). The spinal fluid level of acetylcholine has not been demonstrated to be significantly different between alcoholics and controls. Alcohol has, however, been shown to cause a decline in rat brain acetylcholinesterase, and, furthermore, it inhibits acetylcholinesterase in the minced tissue of cat brain (158). One uncontrolled study has shown that chronic alcoholics have a feeling of fatigue and heightened anxiety, as measured by the Clyde Mood Scale, after administration of the central cholinomimetic drug physostigmine (159).

STUDIES ON BRAIN BIOCHEMISTRY OF DEPRESSIVE AND ALCOHOLIC SUICIDES

Several studies have compared levels of monoamine oxidase (MAO), catechol-O-methyltransferase (COMT), tyrosine hydroxylase (TH), and dopamine-beta-hydroxylase (DBH) in brains of depressed and alcoholic suicides and controls. Some studies have found no significant differences in the level of any of these enzymes, indicating that there may be no biochemical difference between alcoholic suicides, depressed suicides, and controls (160, 161). However, one study did find lower MAO activity among the alcoholic suicides than among depressive suicides or controls (162). This could mean that lowered MAO activity is related to alcohol abuse, or, instead, it could be interpreted that the low activity in alcoholic suicides may reflect lowered activity of monoaminergic pathways. If lowered MAO activity is shown in future research to be consistent with low amine levels through possible feedback mechanisms, this finding would then be consistent with the amine hypothesis for depression. Cochran et al (163) compared levels of 5-hydroxytryptamine (5-HT) in areas of brains of alcoholic suicides, depressed suicides, and controls. He demonstrated no significant differences among any of the diagnostic groups in any of the areas studied. Consistent with this are Robins' findings (161), but not the findings of other researchers who show reduced levels of 5-HT in brains of alcoholic and depressed suicides, supporting the hypothesis that low 5-HT may be involved in their

depression (160, 162). Examining the levels of norepinephrine and dopamine in the brains of alcoholic suicides and depressed suicides, others have found no significant change from controls (161, 164).

Considering possible central electrolyte disturbances, Shaw _et_ _al_ (165) measured brain electrolyes of depressive and alcoholic suicides. Abnormalities in the distribution of electrolytes in severe depression have been found to be an increase in whole body sodium, and an apparent reduction in total body potassium. Most likely, this is secondary to the increased adrenocortical activity with increased cortisol output noted in depressed patients (119, 166). Shaw _et_ _al_ found the depressed suicides to have an increased water content and low concentrations of sodium in the brains of depressives, while the alcoholic group had high water and sodium content and low concentrations of potassium and chloride. This is consistent with the total body compositions of the depressives from other studies, but the importance of these findings is not established.

PSYCHOPHARMACOLOGICAL STUDIES COMPARING CHANGES IN ALCOHOLISM AND DEPRESSION

Only a few biochemical studies have directly compared alcoholics with depressed patients in an attempt to learn more about alcoholic depression, or possibly discover common etiological mechanisms. As discussed, depressives have been shown to have increased total body residual sodium, and decreased potassium when compared with controls. Mac Sweeney (167) performed a study *in vivo* in an attempt to discover whether the abnormalities in body composition seen in severe depression were also present in alcoholics. Although he could not demonstrate any differences in electrolytes between the alcoholics and controls, he did find that both depressives and alcoholics had significantly lower total tryptophan levels when compared with controls.

Such findings suggest testing the prophylactic value of L-tryptophan in preventing recurrent depression and recurrent alcohol abuse. Other studies have also shown a low plasma concentration of L-tryptophan in depressed patients (168-170). Free plasma tryptophan concentration is known to be an important determinant of brain 5-HT turnover, as the rate of brain 5-HT synthesis is substrate dependent. Furthermore, the administration of tryptophan has been shown to increase the amount of functional 5-HT in the brain (169, 170). The decreased level of plasma free tryptophan in the perimenopausal period has been implicated as contributing

to the increased incidence of depressive illness at menopause (169). L-tryptophan has also been found to enhance the effect of MAO inhibitors in treating depression (168). It is conjectured that in alcoholism, withdrawal of alcohol enhances tryptophan pyrrolase (an enzyme which metabolizes tryptophan) activity, whereas, in depression, elevated plasma cortisol levels enhance tryptophan pyrrolase activity yielding a decreased availability of tryptophan for brain 5-HT synthesis (154).

Takahashi et al (154) studied CSF biogenic amine metabolites in alcoholics and unipolar depressives. They demonstrated pronounced suppression of HVA in alcoholics with withdrawal symptoms, which later returned to normal after clinical recovery. Yet, the level of HVA in depressives was the same as controls. Furthermore, they found significant decreases in CSF 5-HIAA in the depressives, but, no significant decrease in the alcoholic group as a whole but some in those alcoholics showing withdrawal symptoms. The decreases in the latter group were sustained until four weeks later when withdrawal symptoms were markedly recovered.

Since blood platelets accumulate, store, metabolize, and release serotonin with a mechanism very similar to central serotonin containing neurons, Banki (171) compared the blood 5-HT content of alcoholics and patients with affective disorder. He found that the depressive's blood 5-HT levels were significantly lower than those of controls, while alcoholics levels were also lower than controls but not

as low as depressives. He states, in agreement with Ballenger _et al_ (151), that alcohol can acutely antagonize such a deficiency as it can act as a serotonin agonist by slowing serotonin degradation, thereby, causing further release of serotonin through alcohol's metabolite acetaldehyde.

Still other enzyme activities have been investigated. Some investigators, evaluating serum dopamine-beta-hydroxylase (DBH) activity (which catalyzes the final step in norepinephrine biosynthesis) in relationship to mood states during alcohol ingestion, have discovered that low pre-drinking activity of serum DBH correlated with fewer positive mood states following alcohol (172). Yet subjects with higher DBH activity felt significantly better and less intoxicated and drank more alcohol. Sullivan _et al_ (172) did not find serum DBH activity of chronic alcoholics to differ from controls, although, previous reports had shown it to be elevated. Some investigators have found that alcoholics have chronically and significantly low platelet MAO activity when compared with controls (172, 173). This is consistent with the low MAO activity found in the brains of alcoholic suicides mentioned earlier. Brown (173) found the lower MAO activity to return to normal after six months of abstinence. However, Sullivan _et al_ (172) found the reduced platelet MAO activity to last for twelve months, the entire length of their study, and suggest that low platelet MAO activity may provide a biochemical index of vulnerability

to alcoholism. Gottfries and collaborators (174, 175) have published data that demonstrate a relationship between low monoamine oxidase activity in the brain and suicidal behavior among alcoholics.

DEPRESSION, ALCOHOL, AND ENDOCRINE RELATIONSHIPS

Various hormonal changes have been implicated in depression. Intense use of cortisol has been associated with the onset of depression (121). There is also a reported frequent increase in adrenocortical activity with increased cortisol secretion in depressed patients (119, 166). Studies with animals and humans have shown plasma cortisol to be increased substantially with acute alcohol ingestion, normal with chronic alcohol administration, and highest during the withdrawal of alcohol (134, 140, 144). One can speculate that the depression found during alcohol withdrawal could be associated with this substantial rise in plasma cortisol. The increased adrenocortical activity after alcohol use is dependent on adrenocorticotrophic hormone (ACTH) secretion and there is some suggestion in human studies that alcohol may have a direct releasing effect on pituitary ACTH (140). Chronic ingestion of alcohol has also been shown to alter the normal circadian rhythm of corticosterone in mice and in humans (176). Irregular diurnal rhythms have been found in depressed patients, as well as abnormal cortisol suppression following dexamethasone treatment (166, 177). Alcoholics have also shown an abnormal suppression of cortisol following dexamethasone, which could reflect a disturbance of central regulation of hypothalamic, pituitary, and/or adrenal activity (178). These results provide further evidence of a possible common pathogenetic pathway in depression and alcoholism.

Studies have shown depressed patients to have mild thyroid hyperactivity while alcoholic patients including depressed alcoholics have normal or relatively hypothyroid function (140, 179). However, one study demonstrated the free thyroxine of depressed alcoholic men in acute withdrawal to be substantially greater than normal controls (180). Some recent reports suggest that the administration of thyroid hormone potentiates the action of tricyclic antidepressants in depressed patients (119, 166). The increase in serum thyrotropin (TSH) in response to the administration of its releasing hormone protirelin (TRH) appears to be diminished in depressives (119, 166, 180). Further, the intravenous administration of TRH is reported to have a rapid, partial, brief, and beneficial antidepressant effect in women with unipolar depression (119, 180). Loosen _et al_ (180) treated chronic alcoholics with secondary depression with TRH in a double-blind, placebo-controlled study, and they discovered that alcoholics have a significantly lower change in TSH than normal controls indicating a blunted respones, which remains blunted over time. Furthermore, their results indicate that TRH may exert beneficial behavioral effects which are again rapid in onset, partial, and brief--in men in the acute withdrawal state. They found TRH in these patients to have a short-term antidepressant action. Men who showed a blunted TSH response showed more than twice the improvement in depressed mood and symptoms,

than men who did not have such a blunted TSH response.

This is consistent with a hyperdopaminergic state during alcohol withdrawal since there is evidence that hyperactivity of dopamine inhibits the TSH response to TRH. Furthermore, the findings of a low baseline level of prolactin and elevated baseline level of growth hormone are also consistent with this hypothesis since prolactin is considered to be under inhibitory control of dopamine and growth hormone to be stimulated by central dopaminergic activity. It is possible that the blunted TSH response represents a common biological feauture in some alcoholics and some depressed patients which might parallel the genetic relationship, as already suggested, between alcoholism in men and early-onset unipolar depression in women.

Further study of hormonal changes under central dopaminergic control show that postmenopausal depressed patients secrete less growth hormone than non-depressed controls in response to insulin hypoglycemia (166). Langer _et al_ (181) demonstrated peak growth hormone release after a single intravenous dose of amphetamine sulfate to be significantly lower in endogenous depressives and significantly higher in reactive depressives as compared to normal controls, whereas, peak growth hormone release in chronic alcoholics did not differ significantly from controls.

DRUG THERAPY OF DEPRESSION IN ALCOHOLISM

ANTIDEPRESSANT AND ANTIANXIETY DRUGS

With the recognition that the alcoholic population has a high prevalence of depression, researchers have begun to investigate the use of psychotropic drugs in treatment. Some early investigators attempted to combat alcoholic's depression with stimulants (182). They used a combination of D-amphetamine sulfate, pentylenetrazol, and nicotinic acid, and found, in a double blind study, this combination to be effective in the management of depression in seventy-six per cent of patients. However, more recently, investigators have used antidepressant, antianxiety, and combinations of these drugs. The results of these studies have been equivocal. One study tested a variety of antianxiety and antidepressant drugs among a population of alcoholics in which seventy per cent exhibited mild to severe depression as measured on the Zung Scale (36). They found that depression as a symptom decreased over time irrespective of the type of drug regimen employed, with the amount of change of depression proportional to the initial level of depression. Mottin (183), reviewing several studies, found that none of the psychotropic drugs examined attenuated drinking in the depressed or anxious alcoholics, except imipramine with which the alcoholics reported a decreased "drive" for alcohol following a lifting of depression. Viamontes (184) reviewed sixteen British and American studies which used antidepressants and/or phenothiazines in the treatment of alcohol abusers. They

saw a high rate of success (eighty-five per cent) in uncontrolled trials but a very low rate of success in the controlled studies (nineteen per cent). Success or failure in these studies was, of cours, measured by widely different criteria, ranging from complete sobriety to regular visits to an outpatient clinic to simple improvements in anxiety, depression, or other functions. Comparison is at best difficult.

A few studies have reported favorable results in alleviating depressive symptoms with tricyclic antidepressants as compared to placebo or another drug (20, 185-188). Butterworth (185) found seventy-five per cent of alcoholics admitted to a state hospital for detoxification to be clinically depressed by the Zung Self-Rating Depression Scale. In a double blind comparison with placebo, using improvement in depressive symptoms as the criteria for efficacy, imipramine was significantly superior to placebo by the end of the third week. Overall _et al_ (20) discovered amitriptyline to be very effective in alleviating symptoms of anxiety and depression in detoxified alcoholic patients in an uncontrolled study. In a double blind, placebo controlled study, Wilson _et al_ (186) demonstrated imipramine to significantly and substantially improve depression in post-alcoholic female depressives as measured on the Hamilton Rating Scale for depression and Self-Rating Depression Scale. Furthermore, the most substantial improvement occurred during the first two weeks when the physiological depressive symptoms showed

the most benefit, again, from imipramine. Nagy (187) treated four alcoholics who related their drinking to episodic anxiety which was not reactive to any major life events with tricyclic antidepressants, and he found their dysphoric episodes to be seemingly benefitted over a short period of two to four weeks.

Some studies have compared the efficacy of tricyclics to benzodiazepines, or compared the combination to placebo (37, 188-190). Butterworth et al (188), in a double blind controlled study among anxious, depressed hospitalized alcoholics, compared diazepam with doxepin (an antidepressant structurally related to both amitriptyline and imipramine). Patients in the doxepin group showed a statistically significant greater improvement in anxiety, depression, somatization, and guilt. However, in another double blind study (189) involving each drug as well as placebo, each group showed significant improvement over the course of a three week period without any statistically significant difference. Kissin and Gross (190, 191) discovered the majority of alcoholics in their clinic to have high levels of both anxiety and depression compared with a normal population. Therefore, they compared chlordiazepoxide and imipramine--alone and in combination, with placebo. The tranquilizer-antidepressant combination was the most effective in alleviating symptoms of anxiety and depression. However, this contrasts with the results of Shaw et al (37) who demonstrated no

significant differences between depressed alcoholics given the combination or placebo in a double blind study. Depression abated in both experimental and placebo groups with time.

Several studies have shown tricyclics to be ineffective in treating anxiety or depression or both in alcoholics (192-196). Four of these were double blind trials comparing tricyclics with placebo, and used, as their criteria of improvement, abstinence from alcohol or good clinic attendance (193-196). In none of these studies was the antidepressant drug found to be superior to placebo, and so, the idea that an antidepressant drug would help to decrease the drop out rate, improve clinic attendance, or improve abstinence was not substantiated. One study used improvement in anxiety and depression as criteria for success, and again, no difference could be demonstrated (192).

Since phenothiazines have been found to be effective against agitated depressions (191), five studies have attempted to evaluate the effectiveness of phenothiazines in treating depression and anxiety among alcoholics (20, 194-197). Three double blind studies using abstinence or clinic attendance as their criteria for effectiveness found no significant differences between drug groups and placebo groups (194-196). However, two studies, using improvement in anxiety and depressive symptomatology as criteria for success found phenothiazines to be significantly better than placebo

(20, 197). Overall et al (20) showed meroridazine at a very low dose level to be an effective drug for relieving anxiety and depression in detoxified alcoholic patients. Huague et al (197) found, in a double blind placebo controlled study with already detoxified alcoholics, that both placebo and active medication groups improved symptomatically during the four week program, but that the thioridazine group had significantly more improvement in sleep disturbance (early, middle, and late insomnia) and anxiety. A few uncontrolled studies have also described a combination of perphenazine (a phenothiazine) and amitriptyline to be effective in the treatment of agitation and depression of alcohol withdrawal (198, 199). One isolated study showed a combination of tranylcypromine (a MAO inhibitor) and trifluoperazine (Stelazine) not to be effective in decreasing the drop out rate of alcoholics from their clinic (200).

Although there is some evidence that tricyclics and phenothiazines are effective in reducing anxiety and depression in alcoholics, these drugs appear to be ineffective in improving clinic attendance or promoting abstience. It is interesting that in several of these studies, relief of anxiety and depressed symptoms occurred after only two to three weeks of treatment suggesting that the observed changes are the product of an anticholinergic action. As earlier discussed, some hypotheses of depression suggest a cholinergic imbalance with high levels of acetylcholine

in the brain. Trihexyphenidy, an anticholinergic drug used to treat Parkinsonism, has been shown to reduce excessive fluid and alcohol intake in the rat (183). Further research in this area is warranted.

Several problems exist in all of these studies especially insufficient recognition of the heterogeneity of alcoholism and depression. Most of the clinical trials of antidepressants included alcoholics with depressive symptoms, however, no effort was made to distinguish the diagnostic subtypes of depression--primary, secondary, unipolar, or bipolar. Using such a mixed group for the therapeutic population may obscure results.

LITHIUM TREATMENT OF ALCOHOLISM AND DEPRESSION

Recent research has shown lithium to be an effective prophylactic agent against recurrent attacks of depression (201). It has been shown to improve mood in patients with recurrent depression, but, not those with chronic apathetic depression (202). Flemenbaum (201) suggests that alcoholism is a precursor of affective disorders and that the subpsychotic mood swings present in some individuals may be approached by self medication with alcohol. Because of the association between alcoholism and depression, some researchers have begun to investigate the use of lithium in alcoholism.

There are a number of studies attesting to the effectiveness of lithium in modifying the drinking habits of alcoholics (203-207). Four of these studies were placebo controlled, double blind studies conducted over a period of a year or more (203-206). Each showed lithium therapy to be significantly more effective in reducing drinking, incapacity, and hospital admissions in chronic depressive alcoholics. The non-depressive patients showed no significant benefit. However, after treatment for one year there were no significant differences in depression ratings between the depressed placebo and the depressed active drug groups. Only two reports in the literature did not find lithium effective in reducing the symptoms of alcoholism (201, 208). In these uncontrolled studies, the study period may have been too short to illustrate benefit.

Sellers et al (209) also discovered lithium to be effective in mild alcoholic withdrawal, in which the drug diminished subjective symptoms and normalized performance on a motor tracking task. Animal studies using rats did not collaborate this (210). Ho and Tsai (210) did, however, find lithium to produce a significant reduction in alcohol preference and volitional consumption in alcohol dependent rats under a forced drinking schedule. These authors also found levels of brain acetylcholine to have a good correlation with these behavioral observations. Lithium has been demonstrated to inhibit the uptake of choline leading to a decrease in the synthesis concentration and the release of brain acetylcholine (211-213). Thus, these studies have shown a possible role for lithium in modifying the drinking habits of chronic depressive alcoholics that may be secondary to alteration of central cholinergic mechanisms.

Careful consideration to the possible dangers in prescribing antidepressants or lithium to actively drinking alcoholics must be made. Most tricyclic antidepressants interact poorly with alcohol with changes in the autonomic nervous system and the development of heart irritability which can be life threatening (214). Also the therapeutic blood levels for lithium occupy a very narrow range; at doses above two milliequivalents per liter, life threatening consequences can occur, including convulsions and death (215, 216). The blood levels for lithium are not only dependent

upon the dose of the drug, but, also, increase markedly during periods of salt depletion; therefore, an actively drinking alcoholic who neglects his salt intake or developes persistent vomiting could rapidly become lithium toxic. Careful follow-up of all patients on lithium is mandatory.

CONCLUSIONS

A strong association exists between alcoholism and depression. A majority of alcoholics are depressed, and the depression is positively associated with drinking episodes, increased alcoholic morbidity, suicide, and decreased treatment success. There is evidence of a genetic link between alcoholism and unipolar depression, but not bipolar disease. The depression in alcoholics is still heterogeneous. Some alcoholics have a chronic unremitting depression, while others, a periodic course. It can be a primary unipolar depression preceding the onset of alcoholism or a secondary depression consequent to the alcoholism. Of course, frequently, it is impossible to differentiate causality or even the sequence of events. Still, it is important to continue to attempt to classify the various types of depression found in alcoholism, as this may be important in formulating the most successful treatment strategies for each case.

Research on the biochemical mechanisms underlying depression, alcoholism, and depression in alcoholism is still beginning. However, already it is known that the biochemical and hormonal changes in these disorders have some similarities, lending support to the possible role for the "amine hypothesis" and "serotonin hypothesis" in alcoholism. There is also evidence of a possible link between central cholinergic metabolism and alcoholic drinking

behavior, especially since the early positive response to tricyclics is unlikely a catecholamine but rather an anticholinergic effect. Further research into brain catecholamine and serotonin metabolism in these disorders is warranted as well as exploration of possible defects in cholinergic metabolism.

Conflicting reports have been published concerning the efficacy of tricyclics in the treatment of alcoholism. Future efforts should be directed toward determining subgroups of depressed alcoholics, as has been done with unipolar depressives, which respond best to imipramine or to amitriptyline as determined by urinary MHPG levels and CSF 5-HIAA levels. Thus far, the use of lithium therapy in chronic alcoholism is promising, with the majority of studies showing a decrease in alcohol consumption and morbidity among depressed alcoholics after lithium use for an extended time period. Puzzling, however, is that this is not associated with a concomitant decrease in the depression of the patients studied. If such depression can be alleviated by drug therapy, it will have implications on the long term management of depressed alcoholics. Hopefully, as more is learned about the treatment of depression in alcoholism, we may be able to more effectively decrease the prevalence and morbidity of alcoholism in the general population.

SUMMARY

The literature--based on psychological, epidemiologic, genetic and biochemical data--is reviewed which establishes an association between alcoholism and depression. The prevalence of depression in the alcoholic population is at least fifty per cent. Such depression is positively correlated with drinking episodes, increased alcoholic morbidity, and less successful treatment in alcoholism. The depression which alcoholics experience is similar to that which unipolar depressives experience, although perhaps less intense. Contrary to popular opinion, intoxication increases depression for alcoholics rather than relieves it. A strong association between alcoholism, depression, and suicide has been demonstrated--with an average lifetime suicide risk of thirty per cent for alcoholics.

Strong evidence for a genetic relationship between alcoholism and unipolar depression has also been established, with both disorders found in the same families--depression more often manifest in females and alcoholism in males. In studying secondary depression, the primary illness most often found is alcoholism. There is no evidence for an association between alcoholism and bipolar affective disorder.

Although research is sometimes conclicting, there is evidence of abnormal brain catecholamine metabolism among alcoholics, indicating a possible link to the "amine hypothesis"

of depression. Other evidence supports the possibility of low brain serotonin among alcoholics, consistent with the "serotonin depression" hypothesis. There is also preliminary evidence that endocrine abnormalities noted in depression may exist among alcoholics.

Results of attempts to treat alcoholism with tricyclic antidepressants and phenothiazines are equivocal; however, both can be effective in reducing the anxiety and depression in some alcoholics. More effective in modifying drinking habits of chronic depressive alcoholics is lithium; however, it is ineffective in alleviating depression in these people.

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--an old saying, and a true; much drinking, little thinking.

Jonathan Swift 1667-1745

I have very poor and unhappy brains for drinking. I could well wish courtesy would invent some other custom of entertainment.

Shakespear. Othello.

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