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## TILAK VENKOBA RAO ORATION

# SEROTONIN AND ITS METABOLITES AS BIOLOGICAL MARKERS OF SUICIDAL BEHAVIOUR[1]

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Honourable members, learned guests, members of the Indian Psychiatric Society and friends, it is a great privilege that I have been selected to deliver the prestigious Tilak Venkoba Rao Oration. I wish to thank the Indian Psychiatric Society for bestowing this award. I pay my respect to 'Tilak' worthy son of worthy parents Professors Venkoba Rao and Parvathi Devi, in whose memory this oration has been instituted for younger members of the society.

I wish to thank my alma mater - King George's Medical College Lucknow and all my teachers who have guided me to become a psychiatrist.

This recognition from the scientific community and encouragement from my seniors will spur me to even greater hard work in my research and persuit for that truth which is the Goddess of all scientists.

## INTRODUCTION

The importance of suicide needs no emphasis; it is by far the most frequent cause of death from mental disorders, and is among the ten leading causes of death the world over. Earlier research focused mainly on psychological factors in the etiology of suicidal behaviour; biological factors were thought to be non-existent, or at least unimportant. The search for biological markers or etiology of suicidal behaviour was spurred partly by the inability of psychologically oriented studies to adequately explain and predict suicidal behaviour.

## OVERVIEW OF BIOLOGICAL MARKERS OF SUICIDAL BEHAVIOUR

The search for a biological marker for suicide was initiated by the reports of Bunney *et al.* (1965, 1969) who found high levels of urinary 17-hydroxycorticosteroids in suicidal depressives though Levy & Hansen (1969) failed to replicate this. As shown in Figure 1, the important biological markers elucidated so far pertain to Neuroendocrine function and to Monoaminergic neurotransmission.

Thoughactivation of the Hypothalmic-Pituitary-Adrenal axis (increasedcortisol levels,abnormal Dexamethasone Supression test) has been found to be more common in suicidal than in non-suicidal depressed patients (Traskman *et al.*, 1980; Caroll *et al.*, 1981; Banki *et al.*, 1981, 1984; Coryell and Schlesser, 1981; Reus, 1982; Targum *et al.*, 1983; Lopez-Ibor *et al.*, 1985) results in nondepressed suicide attempters have been conflicting. An abnormality of the Hypothalmic-Pituitary-Thyroid axis in the form of a blunted Thyroid Stimulating Hormone response to Thyrotropin Releasing Hormone has been related to an increased incidence of completed suicide (Linkowoski *et al.*, 1984).

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Studies of monoamines and monoamine metabolites in the brains of patients who commited suicide were first published in the 1960's aiming to elucidate biological factors in depression which was believed to be the cause of suicide (this is partly true - it is the commonest disorder underlying suicide). In relation to the Dopaminergic system. Traskman *et al.* (1981), Montgomery and Montgomery (1982), and Agren (1983) showed that suicidal depressives had lower CSF homovanillic acid (HVA) the major dopamine metabolite, than nonsuicidal ones. There is reason to believe, however, that low CSF HVA as a predictor of suicide may be limited to depression (Traskman *et al.*, 1981; Ninan *et al.*, 1985) and, therefore, perhaps related to it rather than to suicidal behaviour as such. Further, it may be limited among depressives prone to violent attempts (vide infra) only (Banki *et al.*, 1984). Van Pragg *et al.* (1990), in their stimulating presentation of a hypothesis of the relation between monoamines and abnormal behaviour, have offered evidence to support their view that low dopaminergic activity is related to motor retardation and inertia irrespective of the diagnosis. Whether low CSF HVA is a better predictor of suicide than low CSF 5-hydroxyindoleacetic acid (5-HIAA) or vice-versa is not clear (Banki *et al.*, 1984; Roy *et al.*,1986).

As regards the Noradrenergic system, only a few studies have investigated CSF levels of 3-methoxy-4-hydroxy phenylglycol (MHPG), the major noradrenaline metabolite, in relation to suicidal behaviour, and the findings have been conflicting.

Initially, Serotonergic system markers were studied in relation to depressive behaviour, but later research also focused on suicidal behaviour as such and considerable, cosistent evidence has accumulated relating them to it, as discussed in this paper.

## WHY CSF 5-HIAA?

Although various markers of serotonergic activity in the brain are known and have been studied in relation to suicidal behaviour as well, the most commonly studied marker is CSF 5-HIAA (it was the focus of our work, too) because for prediction of suicide, studies have to be antemortem and here the brain is not usually accessible directly; CSF is not very difficult to obtain for study and is a far better representative of brain function than blood or urine. The extent to which marker in the latter two reflect serotonergic neurotransmission in the brain is not clear. 5-HIAA is by far the major metabolite of serotonin, and its levels in the CSF have been shown to correlate with sertonergic function in the brain.

However, CSF 5-HIAA as a marker or predictor of suicide has certain disadvantages viz. hospitalization is required for lumber puncture; a highly standard procedure has to be adopted as nuemerous factors affect its levels (vide infra); a drug-free period is required prior to drawing the sample and lumber punctures do not consent to it.

The present paper, being concerned with the prediction of suicide, will emphasize on CSF 5-HIAA related finding, though briefly reviewing other markers and post-mortem studies.

## FACTORS TO BE CONSIDERED IN INTERPRETING THE STUDIES

### 1. DIAGNOSIS

A) The diagnostic category of suicidal subjects is important because abnormalities in relation to monoamine activity have been found in nonsuicidal psychiatrically disordered patients, especially depressives, as well. Low CSF 5-HIAA in depression has been reported by

numerous studies (Post *et al.*, 1980- review of 15 studies; Gibbon and Davis, 1985). A greater incidence of low CSF 5-HIAA is found in major depression than in other types (van Pragg and Plutchik, 1984); melancholic than in non-melancholic depression; delusional than in non-delusional depression and more severe melancholic depression (van Pragg *et al.*, 1986)

Thus, it is also important to know the subtype and severity of the depression.

B) van Pragg *et al.* (1986) argued that the retrospective diagnosis of Nondepressed suicide attempter was unreliable because a depressive syndrome prior to the attempt is very common (Beskow, 1979; van Pragg, 1982a,b), and the rated severity of depression decreases substantially after the suicide attempt ( van Pragg and Plutchik, 1985) the hypothetical cathartic effect of attempted suicide.

## 2. REPRESENTATIVENESS OF THE SAMPLE

Most research in biological psychiatry is conducted at tertiary referral centres and it is usually not known how far the sample represents the usual patients. Treatment resistant patients and otherwise complicated cases who may be biologically deviant are probably over-represented in such samples (Asberg *et al.*, 1986 a).

## 3. CRITERION FOR SUICIDAL BEHAVIOUR

Three indicators of suicidal behaviour have been used:

1) suicidal attempt

2) completed suicide

3) rating scale of suicidal tendency

Which of these is used makes all the differences. Most studies (including my own work) focused on suicidal attempters. However, there is an important difference between suicide attempters and completers. Only about 2% of suicide attempters actually commit suicide in the first year after the attempt (Ettlinger, 1975). In most cases it can be determined that the subject did not definitely intend to die.

Most rating scales view suicidal ideation and attempts as a continuum of increasing severity of suicidal tendency. Though this may be justified in the assessment of suicidal risk, biological markers of suicidal thoughts may be very different from those of actual attempts (Asberg *et al.*, 1986 a). Notably, Asberg *et al.* (1976) found that CSF 5-HIAA was correlated with suidides attempts but not to suicidal ideation or rated suicide risk and this has been found in my studies of depressed and schizophrenic suicide attempters as well, though others found correlation with both, as discussed below.

## 4. RECENT OR LIFETIME SUICIDE ATTEMPTS

It is important to distinguish a correlation with recent suicidal attempts which may reveal a state marker, from correlation with lifetime suicidal attempts which may yield a trait marker.

## 5. SERIOUSNESS OF THE SUICIDAL ACT

Suicidal acts have frequently been divided into violent and nonviolent depending on the method used (Paykel and Rassaby, 1978). Drug overdose and superficial wrist cutting are nonviolent suicide, while all other methods are trait violent.

van Pragg *et al.* (1986) has convincingly argued that the strength of the intent to die is also determined by choice of a situation in which the chances of being rescued are lesser. These two have been combined in the Risk-rescue Scale of Weisman (1972) and van Pragg *et al.* (1986) using this scale found no significant difference in scores on it between subjects simply classified as violent and nonviolent suicides.

## 6. FACTORS AFFECTING CSF 5-HIAA CONCENTRATION

These factors, which have to be controlled for any meaningful study include age (Asberg & Bertilsson, 1979) - higher with increasing age ; sex (Asberg *et al.*, 1973; Asberg and Bertilsson, 1979; Roy et al., 1990) - lower in males; body height (Wode-Helgodt and Sedvall, 1978; Asberg and Bertilsson, 1979; Curzon *et al.*, 1980; Banki & Molnar, 1981) - lower in taller subjecs; time of the year ( Asberg *et al.*, 1981; Losonczy *et al.*, 1984) - higher in winters; time of the day (Nicoletti *et al.*, 1981; Garrick *et al.*, 1983) - higher at night; physical activity (Fotherby *et al.*, 1963; Post *et al.*, 1973); Various physical diseases (Anderson & Roos, 1969; Johansson & Roos, 1967; Anderson *et al.*, 1981; Hallert *et al.*, 1982); antipsychotic drugs (Bjerenstedt *et al.*, 1977; Gomes *et al.*, 1980; Gattaz *et al.*, 1982); antidepressent drugs (Bowers, 1972; Asberg *et al.*, 1973; Post & Goodwin, 1974; Muscettola *et al.*, 1978; Traskman *et al.*, 1979; Bertilsson *et al.*, 1980) - Lower levels; dexamethasone (Banki *et al.*, 1981) - Higher levels; diet (Curzon *et al.*, 1972; Asberg *et al.*, 1986 b); position of the patient for lumbar puncture (Sedvall & Oxentierna, 1986); intervertebral space used (Nodin *et al.*, 1982) - lower in lower space; amount of CSF drawn (Asberg *et al.*, 1986b); analytical method used (Sjoquist & Johansson, 1978) - Mass fragmentography is superior to spectrofluorometry (Asberg *et al.*, 1986b) and CSF pressure and flow (Post *et al.*, 1973 a).

Diurnal and circannual variation of serotonergic activity in the brain has been directly demonstrated (Carlsson *et al.*, 1980)

Postmortem brain studies of CSF serotonergic activity are affected by similar factors including time and mode of death, time to discovery of the body and autopsy (decay of monoamines and their metabolites), and drug treatment.

## 7. BASAL CSF 5-HIAA AFTER PROBENECID/SULFINPYRAZONE

Administration of probenecid or sulfinpyrazone blocks the exit of 5-HIAA from the CSF and the accumulation of 5- HIAA in the CSF indicates serotonin degradation in the CNS. Though most studies have measured only basal 5-HIAA, van Pragg used probenecid in several studies (e.g., van Pragg, 1977, 1982a, 1982b, 1983) as did Post *et al.* (1980), and we have used sulfinpyrazone in one study.

## CSF 5-HIAA AND SUICIDAL BEHAVIOUR

Early studies of CSF 5-HIAA in depression found it to be lowered but did not note any psychopathological difference between patients with or without decreased CSF 5-HIAA except higher anxiety ratings in those with low CSF 5-HIAA (van Pragg, 1986a). The first finding of correlation between suicide and a biological marker in the CSF occured to some extent by chance. Asberg *et al.* (1976) in Sweden, Who studied CSF 5-HIAA in depressives and found lower values in some patients, searched for clinical differences in the two groupsof patients, and unexpectedly found an increased incidence (40% in index episode in low CSF 5-HIAA group vs. 15% in normal CSF 5-HIAA group) of suicide attempts especially

**Table 1 : Studies of CSF 5-HIAA as marker of Suicidal Behaviour**

| WORKERS | SAMPLE | ASSESSMENT OF SUICIDALITY | FINDINGS OF CSF 5-HIAA |
|---|---|---|---|
| Asberg et al. (1976) (Sweden) | Unipolar endogenous & reactive depresives (15 attempters 53 non attempters) | Attempted suicide in index episode | Lower in atempters, significantly only in violent attempters(Sex, height, etc not considered) |
| Vestegaard et al. (1978) | Unipolar & bipolar depressives | Suicide atttempt | No difference (proportion of violent & non-violent attempters not reported) |
| Brown et al. (1979) (U.S.A.) | Primary DSM-III personality disorder (males in military) (11attempters, 11 non-attempters) | Lifetime suicide attempts | Lower in attempters Trivariate relation including aggression. |
| Agren (1980) | 33 unipolar and bipolar depressives | SADS suicidality scale | Negative correlation (Proportion of violent and non violent attempters not reported) |
| Traskman et al. (1981) (Sweden) | 30recentattempters (8 minor depression on New Castle Inventory, 22 other psychiatric disorders excluding schizophrenics substance abuse & organic brain syndrome) 45 healthy controls | Recent suicide attempts | Lower in attempters especially violent (Ruled out sex factor for first time) |
| Leckman et al. (1981) | 132 psychiatric patients | Nurse's ratings of suicidal tendencies | Negative correlation (Proportion of violent & non violent attempters not reported) |
| Oreland et al. (1981) (Sweden) | # 20 depressives,<br># 15 recent suicide attempters (minor depression, anxiety states, personality disorder)<br># 11 recovered depressives<br># 42 healthy controls | Recent suicide attempters | Lower in attempters |

| | | | |
|---|---|---|---|
| Brown et al. (1982a) (U.S.A.) | 12 males (in military) with DSM-III Borderline personality disorder; 5 attempters, 7 nonattempters) | # Lifetime suicide attempts<br># MMPI | Lower in attempters Trivariant relationship included aggression |
| van Pragg (1982a) (Holland) | 203 depresives (54 attempters, 149 nonattempters) | Recent suicide attempts | Lower in attempters, equally in violent & nonviolent attempters |
| van Pragg (1983) | #10nondepressed schizophrenic attempters<br>#10nonsuicidalnondepressed schizophrenics<br># 10 controls | # Recent suicide attempt due to command hallucinations<br># Risk-rescue scale | Normal range but lower in attempters especially those scoring higher on risk-rescue scale |
| Palaniappan et al.(1983) (India) | 40 depressive inpatients | Suicide item of HRSD | Negative correlation |
| Agren (1983) | 110 unipolar & bipolar depressives | SADS suicidality scales | Negative correaltion in unipolar depressives |
| Roy-Byrne et al. (1983) (U.S.A.) | 32 bipolar depressives, 13 unipolar depresives (Mainly treatment resistant patients at a tertiary center) | Lifetime suicide attempts | NoDifference.Nonsignificantly lower in unipolar depressive attempters. |
| Linnoila et al. (1983) | 20 violent offenders | Suicide attempt | Lower in attempters with explosive or antosocial personality |
| Banki and Arato (1983) (Hungary) | 57 female inpatients 2 DSM-III diagnoses (14 major depression-4 bipolar, 7 unipolar, 3 first episodes; 14schizophrenics;4schizophreniform disorder; 13 alcohol dependence,12others;10noviolentattempters,4violentattempters,4nonattempters) | Recent suicide attempt | Lower in violent attemters only |
| Banki et al.(1984) (Hungary) | 141 females including 45 previously reported (36 major depression-unipolar or bipolar, 46 schizophrenic/schizophreniform , 35 alcoholics, 24 adjustment disorders; 18 | Recent suicide attempt | Lower in violent attempters in all diagnoses, lower in nonviolent attempters only in alcohol dependence |

| | | | |
|---|---|---|---|
| | violent attempters; 34 nonviolent attempters) | | |
| Ninan et al. (1984) (U.S.A.) | DSM-III & RDC schizophrenics, 8 suicidal (committed suicide or would have committed) 8 nonsuicidal (no suicidal thought or act) | Lifetime suicide attempts (through clinical and research records) | Lower in suicidal (Proportion of violent & nonviolent attempts not reported) |
| Perez de los Cobos et al. (1984) (Spain) | 21 depressives | # Suicide attempt<br># Suicide item for HRSD<br># AMDP system items for suicidality | Negative ccorrelation with attempta & suicide items of the scales. Equally in violent & nonviolent attempts |
| Roy et al.(1985) (U.S.A.) | 54 DSM-III schizophrenics (27 attempters, 27 non attempters) | Lifetime suicide attempts | No difference |
| Lopez-Ibor et al. (1985) (Spain) | 21 DSM-III MAjor depression with melancholia | # HRSD<br># AMDP system | Negative correlation with aggressive & suicidal behaviour. |
| Lidberg et al. (1985) (Sweden) | # 20 suicide attempters (11 depressives, others anxiety states and/or personality disorders)<br># 39 healkthy controls | Suicide attempt in index episode | Lower in attempters especially violent attempters |
| Berretini et al. (1986) (U.S.A.) | # 15 euthymic bipolar disorders (6 attempters, 9 nonattempters; 3 violent, 3 nonviolent)<br># 30 healthy controls | Lifetime suicide attempt | No difference |
| Pickar et al. (1986) (U.S.A.) | 28 DSM-III schizophrenics (13 attempters, 15 nonattempters) | Lifetime suicide attempts (through records) | No difference (Excluded persistently suicidal patients) |
| Roy et al. (1990) (USA) | #DSM III alcohol dependence (20 attempters, 108 nonattempters)<br>#30 healthy controls | Lifetime suicide attempt on SADS- L | No difference |

by violent methods in the low CSF 5-HIAA group.

The studies of CSF 5-HIAA in relation to suicidal behaviour in depression and other psychiatric disorders are summarized in table 1. All the studies which considered a recent suicidal attempt found a low CSF 5-HIAA. Of studies which used lifetime history of suicide attempts as a variable all but two found low CSF 5-HIAA correlated with it. Even the negative study of Roy-Byrne *et al.* (1983) found low CSF 5-HIAA in suicide attempters when unipolar cases were considered separately. The higher proportion of bipolar patients in their sample then explains the negative overall result. Roy *et al.* (1985), the same group which had reported a negative correlation in schizophrenia between CSF 5-HIAA and lifetime suicidal ideas or attempts (Ninan *et al.*, 1984) failed to reproduce their findings. Roy *et al.* (1990) failed to find lower CSF 5-HIAA in patients of DSM-III alcohol dependence with history of lifetime suicide attempts. Possible reasons for the negative findings include remoteness of the attempts (the correlation with low CSF 5-HIAA is strongest for recent attempts; van Pragg, 1991), small proportion of violent attempts, failure to exclude depression not amounting to DSM-III diagnosis in the non-attempters, and the known relationship between alcohol dependence and depressive disorders. Low CSF 5- HIAA has been found in abstinent alcoholics without suicide attempts (Ballenger *et al.*, 1979; Banki, 1981).

The postmortem CSF study in completed suicides of Kauert *et al.* (1981) found increased serotonergic activity. However, the time of death of suicides and controls was not similar or compensated for, which may explain this anomalous finding. Studies using rating scales for suicidality also found a negative correlation with CSF 5-HIAA.

The studies do not agree on : 1) Whether CSF 5-HIAA is negatively correlated with ratings of suicidality; 2) Whether CSF 5-HIAA is negatively correlated with suicidal ideation with suicidal acts and 3) Whether CSF 5-HIAA is lower in violent than in nonviolent suicides.

The relationship with CSF 5-HIAA to suicidality has been demonstrated in depression, schizophrenia, personality disorders, alcoholism, adjustment disorders, etc. and in relation to current ratings of suicidality, recent suicide attempts, and lifetime suicide attempts. Thus, the evidence for this correlation is quite robust.

I would now like to briefly present my three studies on serotonergic markers in relation to suicidal behaviour. In all three CSF 5-HIAA and platelet/plasma/serum serotonin were chosen as markers of serotonergic neurotransmission but results with the latter being inconsistent are not being discussed here.

The factors affecting CSF5-HIAA levels were controlled: age, sex and body height by matching the study groups and the control group; physical diseases which may affect CSF 5-HIAA were an exclusion criterion; effect of medication by a drug-free period of one week in the first two studies and of two weeks in the third, and in the study on schizophrenics, by excluding those on depot antipsychotics; dietary factors by prohibiting certain foodstuffs and by overnight testing before lumber puncture; effect of physical activity by bed rest and ensured sleep prior to the lumber puncture; time of the day, position of the patient for lumber puncture, intervertebral space used, amount of CSF drawn, handling and storage of CSF, and analytical method used were the same in all subjects.

In all the three studies, psychiatrically normal controls were drawn from patients undergoing spinal anesthesia for surgery who had no past, present, or family history of mental disorder.

The first study, on schizophrenics, used the sulfinpyrazone technique of accumulation of 5-HIAA in the CSF while the other two measured basal CSF 5-HIAA.

The first two studies, on RDC schizophrenics in 1986 and on RDC primary depressives in 1987, were similar, and I will discuss them together. The schizophrenics were evaluated on the Modified Brief Psychiatric Rating Scale (MBPRS; Overall and Gorham, 1962) and the depressives on the Hamilton Rating Scale for Depression (Hamilton, 1960). In addition, the Suicidal Intent Qustionnaire (SIQ) developed and evaluated at our department by Gupta *et al.* (1983), of which team I was also a part, was used in both studies. The questionnaire divides patients into definite communicators (score $< = 5$), partial communicators (score 2-4), and noncommunicators (score $< = 1$). Partial communicators were excluded from the study.

In the study of schizophrenics, 20 definite communicators, 20 noncommunicators, and 10 normal controls were studied. The study on depressives including 15 subjects of each category. Six of the 20 definite communicator schizophrenics had attempted suicide in the index episode (5 violently and 1 nonviolently) while 3 of the 15 definite communicator depressives had done so (2 violently and 1 nonviolently).

The findings supported the following main conclusions :

* The severity of the disorder did not correlate with CSF 5-HIAA levels as shown by absence of a significant correlation with MBPRS or HRSD scores.

* However, CSF 5-HIAA did show a correlation with components of these scales. In definite schizophrenics it was significantly ($p < 0.05$) negatively correlated with the Anxiety-Depression derived variable of the MBPRS, i.e. those with lower CSF 5-HIAA had higher score on the Anxiety-Depression variable. CSF 5-HIAA was significantly negatively ($p < 0.01$) correlated wirh the suicide item of the HRSD in the depressives.

* We concluded indirectly that low CSF 5-HIAA was significantly correlated only with suicide attempts and not with suicidal ideation alone because : in both schizophrenics and depressives, CSF 5-HIAA of suicide attemptors among the definite communicators was significantly less than that of normal controls ($p < 0.05$ for schizophrenics and $p < 0.01$ for depressives; Figure 2 and 3); in both studies, both communicators and noncommunicators and nonattempters among the definite communicators did not have significantly different CSF 5-HIAA than normal controls (Figure 2 and 3); CSF 5-HIAA was not significaantly correlated to SIQ scores in either diagnostic cateegory; when CSF 5-HIAA of definite communicators (with or without a suicidal attempt) was compared with that of non-communicators and normal controls.

In the schizophrenics, there was a maximum trend for CSF 5-HIAA to be lower in definite communicators than in normal controls, though it did not reach statistical significance (Figure 4). In the depressives, CSF 5-HIAA of definite communicators was less than that of non-communicators ($p < 0.01$) and normal controls ($P < 0.001$), while that of noncommunicators was not significantly different from that of normal controls (Figure 5).

In our third study, done in 1988, we moved from questionnaire rating of suicidality that covered both suicidal ideation and attempts with only a few patients having history of a suicide attempt, to a direct study of suicide attemptors. Three groups were evaluated :

1) 23 nonpsychotic nondepressed subjects with a history of recent nonviolent suicide at-

tempt. One patient had also made an attempt in the past.

2) 14 RDC primary depressives (two-third bipolar and one-third unipolar). Eight had recent attempts (two had past attempts as well ) while six had only past attempts (defined as more than 6 months prior to evaluation). Of the total of 18 suicide attempts in this group, 10 were violent and 8 were nonviolent.

3) 10 normal controls

As in the previous studies, severity of the disorder (HRSD scores) did not correlate significantlywith the CSF 5- HIAA. CSF 5-HIAA in the different groups is shown in Figure 6, 7 and 8. These finding suggest that low CSF 5-HIAA is correlated : 1) To suicide attempts irrespective of the presence or absence of depression. 2) More strongly to violent attempts to CSF 5-HIAA than to nonviolent attempts, though significantly to both.

The correlation of suicide attempts to CSF 5-HIAA may apply more so to unipolar depressives as they had significantly ($p < 0.001$) lower CSF 5-HIAA than bipolar depressives (Figure 9) which was also found by Roy-Byrne *et al.* (1983) who analysed unipolar and bipolar patients separately. CSF 5-HIAA, though reported to be low even in those with only past suicide attempts, may be lower in those with recent attempts as among the depressives we found it to be lower in those with recent attempts than in those with past attempts only, though this difference did not reach statistical significance (Figure 10).

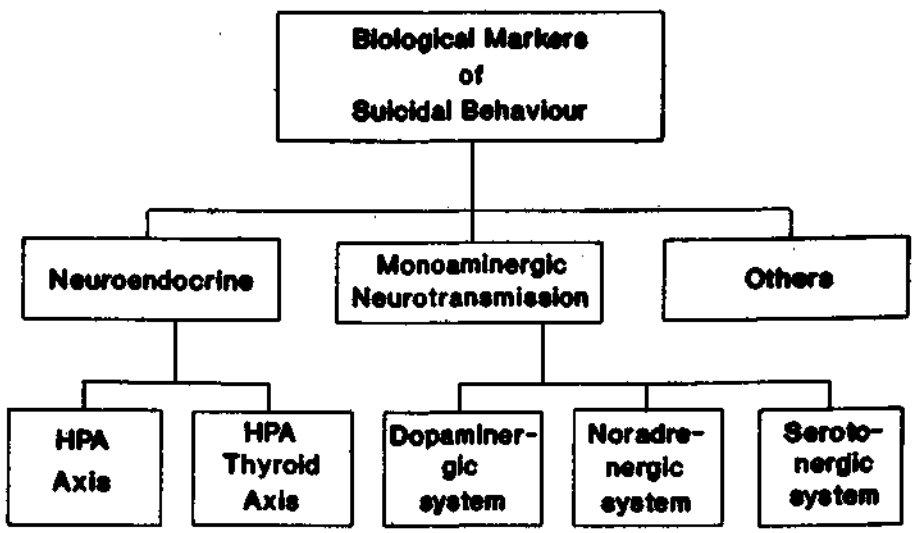


FIGURE 1

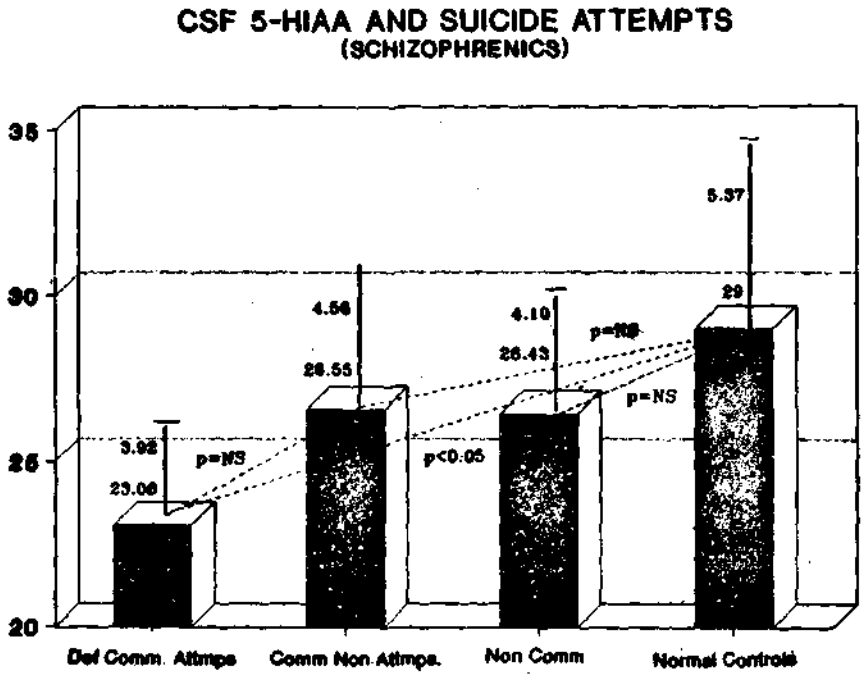


FIGURE 2

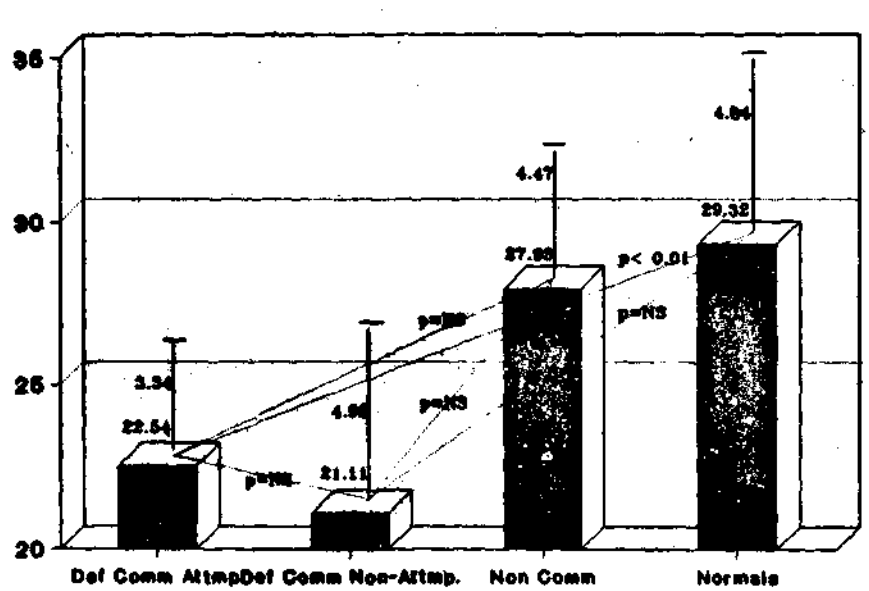


FIGURE 3

CSF 5-HIAA(ng/ml) - SCHIZOPHRENICS

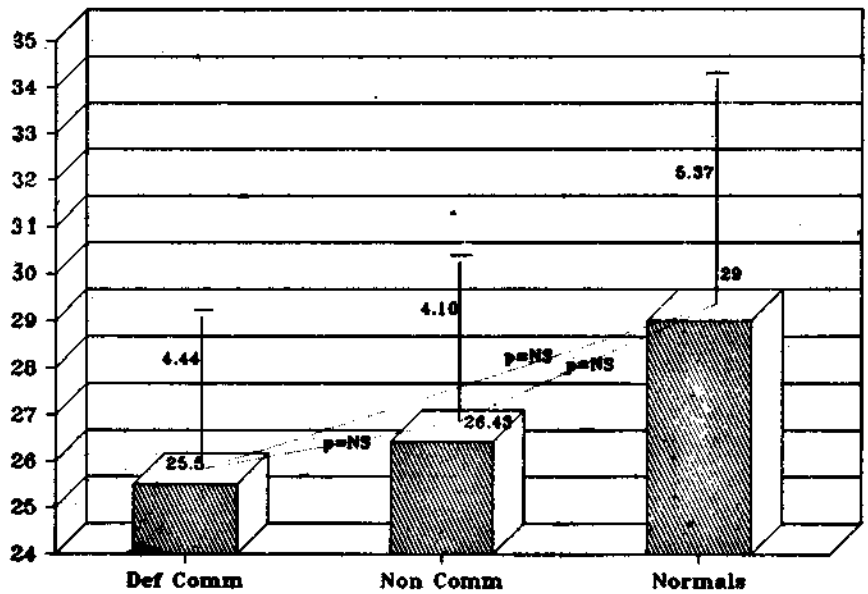


FIGURE 4

CSF 5-HIAA(ng/ml) - DEPRESSIVES

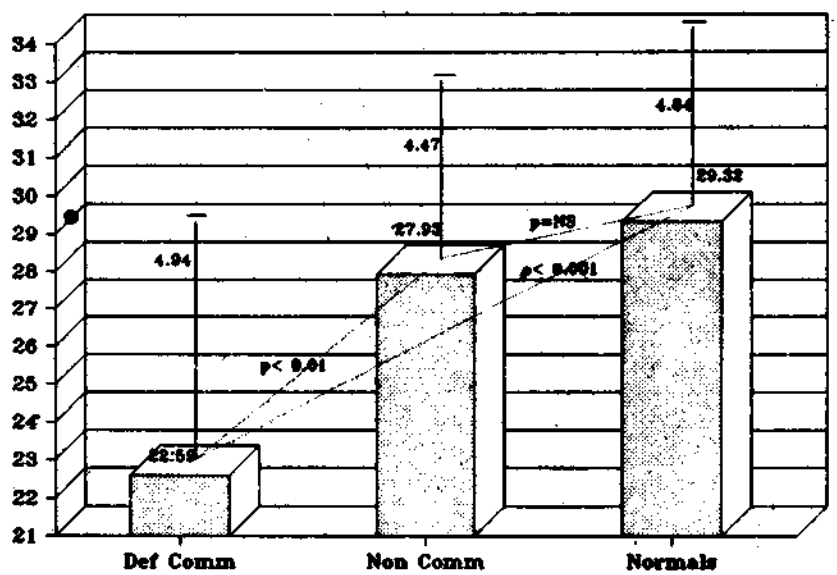


FIGURE 5

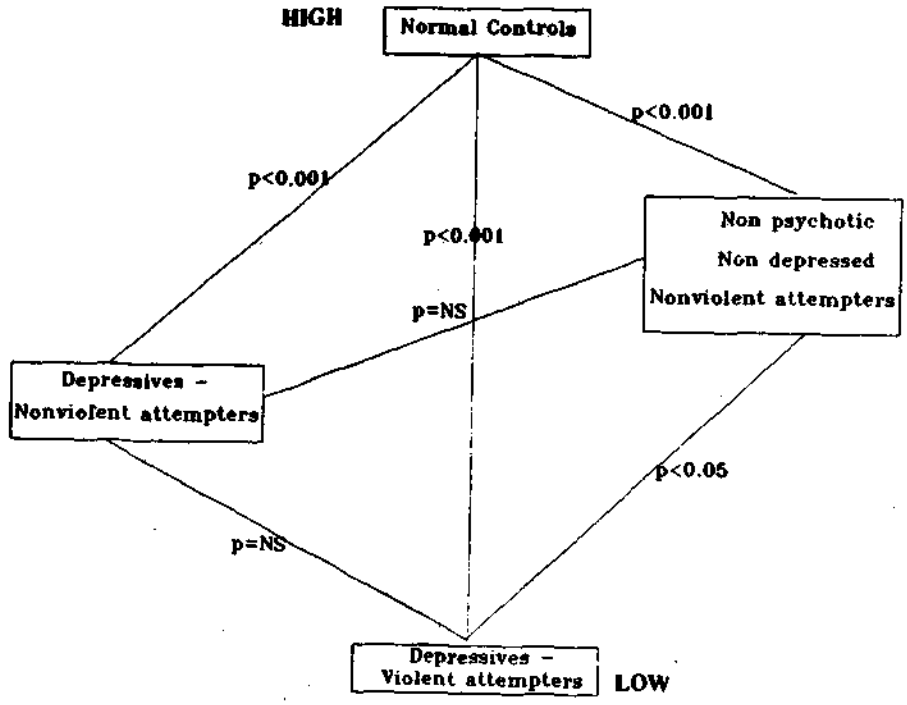


FIGURE 6

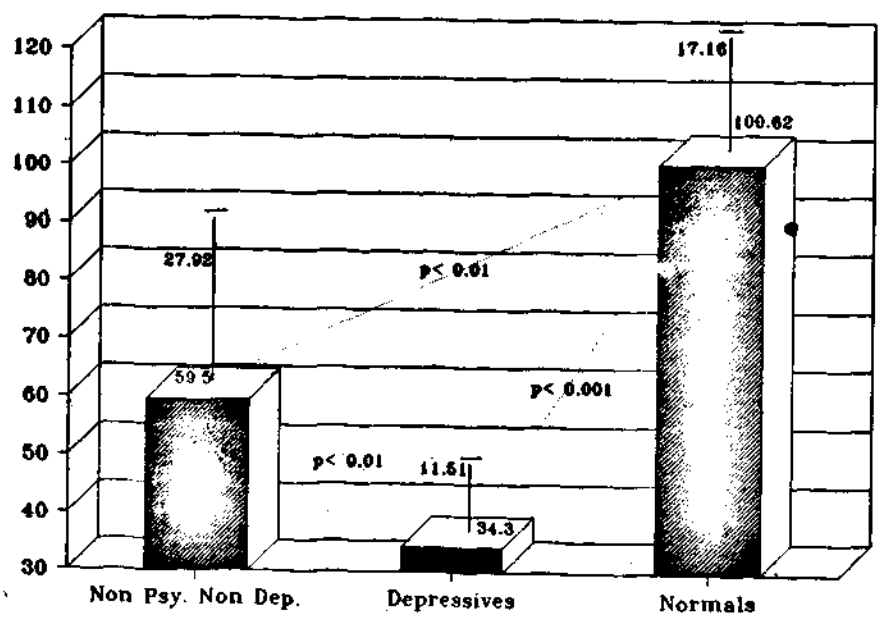


FIGURE 7

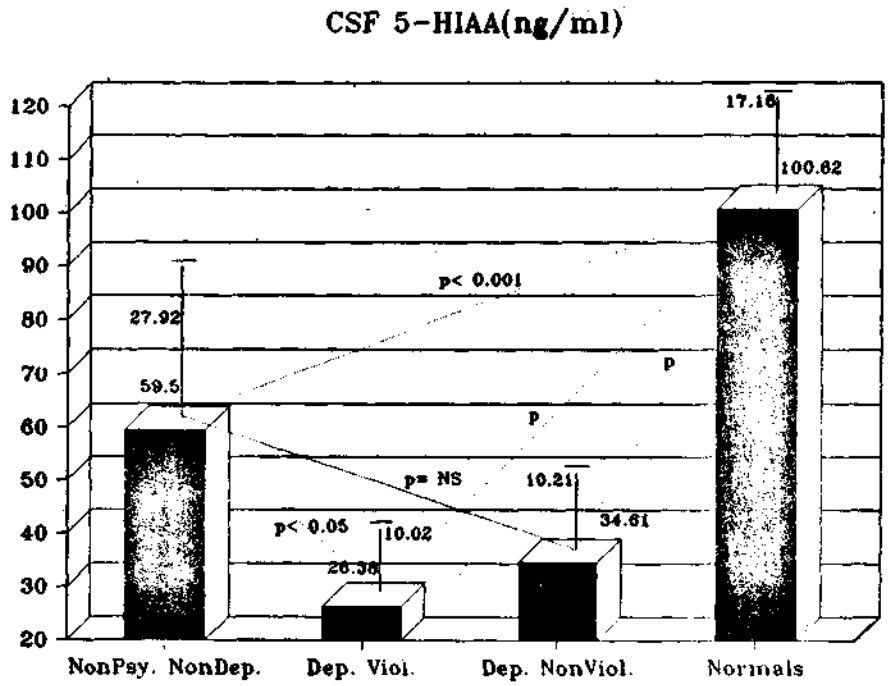


FIGURE 8

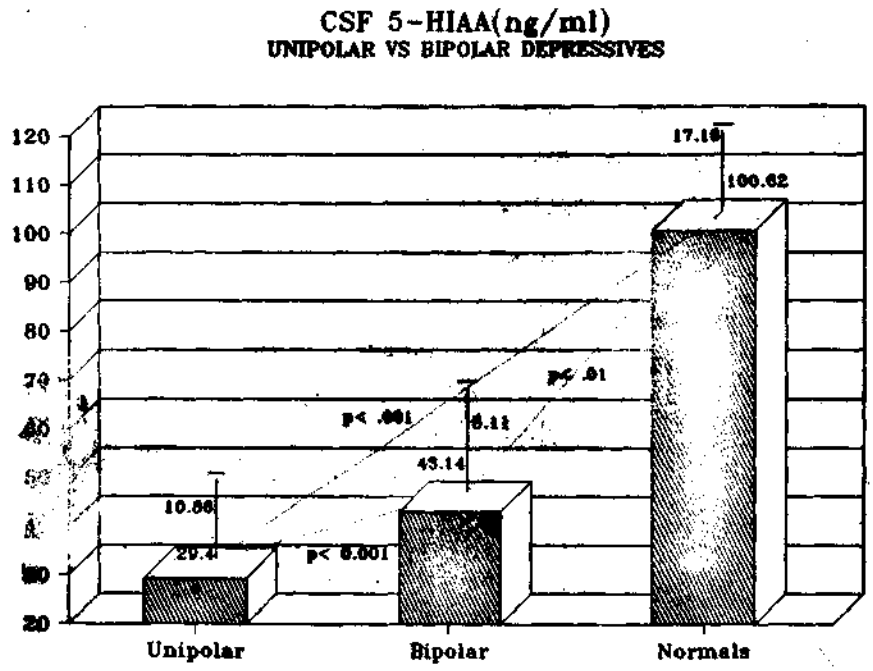


FIGURE 9

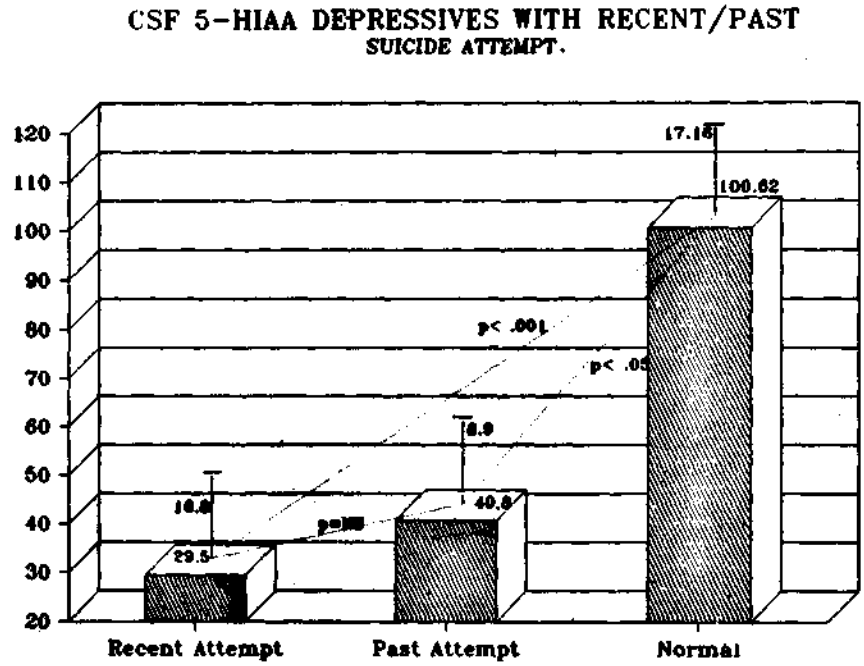


FIGURE 10

## Interaction of Biological and Psychological Factors

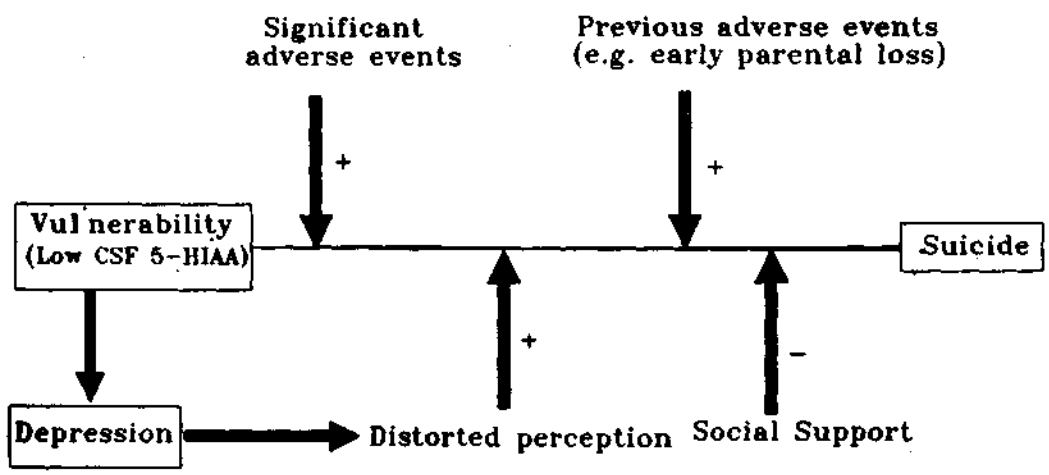


FIGURE 11

## PERSISTENCE OF A LOW CSF 5-HIAA

The assessment is difficult and rarely done because :

1) There is a variation in CSF 5-HIAA concentrations with the time of the year (vide supra). 2) Only few patients are available as most are on drugs and/or do not give their concent for a repeat lumber puncture (once recovered). 3) The few patients available may be nonrepresentative.

Coopen *et al.* (1972) found CSF 5-HIAA levels to be stable in 8 subjects followed for 3-59 weeks. van Pragg (1977) reported that in 50 subjects followed for more than six months, CSF 5-HIAA levels were stable in those with normal levels and in more than 50% off those with low levels, the rest having normalized. Traskman-Bendz *et al.* (1984) who studied 11 subject over 2-7 years found the levels stable in those with normal levels while they rose in those with low levels, though not to normal.

Thus, at present low CSF 5-HIAA appears to be stable over liited periods at least in most patients and if it does increase, it does not return to normal in those periods. It also tends to be similar in each episode of depression.

## LOW CSF 5-HIAA AND SUBSEQUENT COMPLETED SUICIDE

Asberg *et al.* (1986b) followed 76 suicide attemptors for one year and reported that 21% of low CSF 5-HIAA patients committed suicide while 2% of those with normal or high CSF 5-HIAA did so. As mentioned already, CSF 5-HIAA level tends to be similar in subsequent episodes in many patients. Asberg *et al.* (1986b) made repeated estimations in two patients who subsequently committed suicide and in both the CSF 5-HIAA was substantially reduced in the second estimation compared to the first. They suggested that some patients of depression may have low as well as stable CSF 5-HIAA. Perhaps a low and decreasing CSF 5-HIAA may be the most ominous sign of all.

Roy *et al.* (1986 b) also found an increased incidence of completed suicide in suicide attempters with low CSF 5- HIAA. They studied 27 cases of major depression (22 unipolar and 5 bipolar) of which 19 had attempted suicide, 3 by violent and 16 by nonviolent methods of which 4 had recently attempted. The difference between attempters and nonattempters was maximum for 5-HIAA. In one year follow up 4 completed suicide which included 3 of the 7 with low CSF HVA and 2 of the 8 with low CSF 5-HIAA. Lopez-Ibor *et al.* (1985) reported that the two patients with the lowest CSF 5- HIAA levels in their sample had to be later withdrawn from the study due to risk of suicide; both committed suicide within one year of termination of the study of a subsequent relapse. Traskman *et al.* (1981) who followed up 119 patients for about a decade reported that all the 7 who had committed suicide had CSF 5-HIAA below than median.

## SUICIDAL BEHAVIOUR AND OTHER MARKERS OF SEROTONERGIC NEUROTRANSMISSION

**Table 2 Markers Of Serotonergic Neurotransmission**

| | |
|---|---|
| BRAIN | 1. Serotonin |
| | 2. 5-HIAA |
| | 3. [3H] (i.e., tritiated) imipramine binding |
| | 4. [3H] (i.e., tritiated) spiroperidol binding |
| | 5. MAO activity |
| BLOOD | 1. Platelet MAO activity |

2. Ratio of plasma tryptophan or other neutral aminoacids (important determinant of tryptophan transport into CNS; Fernstorm & Wurtman, 1972)

3. Platelet [3H] imipramine binding

4. Platelet serotonin intake

5. Free tryptophan (rate limiting factor in the synthesis of serotonin).

As Table 2 shows, there are several markers of serotonergic activity - its precursor, the parent compound, its binding sites, the enzyme degrading it, and its metabolite, which are related to the brain itself or to the platelet as a model for brain serotonergic activity. As they have little value in themselves as predictors of suicidal behaviour, only some of them will be discussed very briefly.

## BRAIN (Postmortem studies)

The findings are generally consistent with reduced serotonergic activity in the brain of suicide victims.

1. Serotonin

2. 5-HIAA

Some but not all studies have found lower concentrations of serotonin or 5-HIAA in brains of completed suicides, either in the hind brain or in the hypothalamus ( Asberg *et al.*, 1986b-review of 7 studies). Mann *et al.* (1989) who reviewed 12 studies of serotonin and 5 studies of 5-HIAA levess in the brains of suicide victims observed that some, but not all, studies reported modestly lower levels of 5-HIAA and/or 5-HT in the brain-stem but not the cortex. Lloyd *et al.* (1974) estimated serotonin and 5-HIAA in neurons are placed rather than larger segments of brain matter and found lower serotonin concentrations in two of the nuclei. The disparate results of other studies may be due to a failure to study discrete enough segments.

3. [3H] Imipramine binding - It is probably related to and the best marker for the presynaptic serotonin uptake site. Contradictory results (higher, normal or lower binding) have been reported in suicide victims since the initial report of fewer binding sites by Stanley et al. (1982) (Mann *et al.*, 1989-review of 8 studies). Possible methodological reasons for the contradictory findings have been discussed by Mann *et al.* (1989). Whether or not 5-$HT_1$ receptors or their subpopulations are increased in the brains of suicide victims is not clear though Meltzer (1988) has reported an increase in 5-$HT_{1A}$ receptors.

4. [3H] Spiroperidol binding - It is a marker of post synaptic serotonin-2 binding sites. Owen *et al.* (1983) and Staley and Mann (1983) reported increased binding, consistent with decreased serotonergic neurotransmission suggested by the CSF studies. The majority, Though not all, studies have found an increased number of 5-$HT_2$ receptors in the pre-frontal cortex of suicde victims which is consistent with decreased serotonergic activity (Mann *et al.*, 1989).

5. MAO activity - While Gottfries *et al.* (1975) found lower MAO activity in alcoholic suicide victims than in controls, Grote *et al.* (1974) and Mann and Stanley (1984) found it to be similar to controls.

## BLOOD

1. Platelet activity - Buchsbaum *et al.* (1976) reported increased incidence of suicide attempts in subjects with very low platelet MAO

activity and their relatives. Buchsbaum *et al.* (1977) also found a correlation between low activity and suicidal behaviour, but only in those who were also augementers on evoked respnse tests. Gootfries *et al.* (1980) found it lower in depressives with violent suicide attempts than in those with nonviolent or no attempts.

2. Plasma tryptophan/neutral amino acids ratio - Branchey *et al.* (1984) found the ration to be lower in alcoholics especially those with a history of suicidal and aggressive/impulsive behaviour.

## WHAT DOES LOW CSF 5-HIAA REALLY REPRESENT?

This involves several questions :

1. Does CSF 5-HIAA reflect serotonergicc activity in the brain

Bulat and Zivkovic (1971) suggested that CSF 5-HIAA may reflect serotonin turnover in the spinal cord transaction or spinal fluid blockage in man does not affect lumber CSF 5-HIAA levels. However, Stanley *et al.* (1985) in rats have shown a strong correlation between CSF and 5-HIAA. Weir *et al.* (1973) using radioactively labelled 5-HIAA in cats found that 70% of the lumber CSF 5-HIAA was derived from the brain. Banki and Molner (1981) showed that 5-HIAA in lumber CSF correlated well with cisternal CSF.

2. Does low CSF 5-HIAA denote low serotonergic activity?

The findings in relation to other serotonergic markers suggest that this is so, but low CSF 5-HIAA could also be secondary to a hyperactive serotonergic system due to hypersensitive postsynoptic receptors (Aprison *et al.*, 1978) and the issue is unclear (van Pragg *et al.*, 1986).

3. Is CSF 5-HIAA a trait marker or a state marker?

Early studies focused only on the relationship between CSF 5-HIAA and recent suicide attempts but later a correlation with lifetime suicide attempts has been demonstrated by various studies.

Low CSF 5-HIAA seems to be familial to an extent as evidenced by greater incidence of depression in relatives of subjects with low CSF 5-HIAA (van Pragg and De Hann, 1977) and low CSF 5-HIAA in relatives of patients with depression (Sedvall *et al.*, 1980).

Low CSF 5-HIAA has been correlated with certain personality traits. Brown *et al*, (1982) found a correlation between CSF 5-HIAA and the Psychopathic Deviate Scale of the MMPI and noted that subjects with low CSF 5-HIAA had previously shown disturbed behaviour in their childhood. Asberg *et al.* (1986a) noted a correlation with impulsivity on personality questionnaires, and a week but consistent correlation with Eysenck's Psychoticism Scale. Schalling *et al.* (1984) reported that CSF 5-HIAA levels correlates negatively with scores on the impulsiveness scale of the Karolinska scales of Personality. Rydin *et al.* (1982) reported a correlation with high hostility on Rorschach protocols. Intrestingly, in animals, drugs or lesions causing serotonin depletion may produce aggressive or impulsive (disinhibited) behaviour (Soubrie, 1986).

These findings seem to suggest that low CSF 5-HIAA may be a trait marker. On the other hand, the possibility that a decreasing CSF 5-HIAA may represent the highest risk for suicide, the stronger correlation with recent suicide attempts than lifetime attempts, and the change in CSF 5-HIAA levels with time (though perhaps not to normal) indicate a state character of the marker.

In my opinion it is not essential to view low CSF 5-HIAA as either a state marker or a trait marker - it may be both. Like van Pragg *et al.* (1990), I view CSF 5-HIAA as representing not any specific diagnostic categories or even a personality variable, but as a functional psychobiological defect. The biological correlate of this defect (CSF 5-HIAA) could be found both as a trait and a state marker.

4. What is the functional defect of which low CSF 5-HIAA is a correlate?

Psychoanalytic authors have stressed that both depression and suicide are related to aggression directed towards the self (Freud, 1953). Menninger (1933) conceptualized the "wish to kill" as an element of the suicidal act. There is also considerable evidence (Brown *et al.*, 1979, 1982; Valzeli, 1981; Linnoila *et al.*, 1983; Lidberg *et al.*, 1984, 1985; Brown and Goodwin, 1986) linking low CSF 5-HIAA to outwardly directed aggression, especially, like suicide attempts, of an impulsive and more violent type.

Thus, low CSF 5-HIAA may represent the functional defect of a disordered (especially impulsive and violent) aggression and autoaggression, both as a personality trait and as a state, and thus link depression, suicide, and externally directed aggression where it is found. Asberg *et al.* (1986a) noted that the impulsive nature of suicidal or aggressive acts which have been correlated with low CSF 5-HIAA may explain why it appears to be related to suicidal acts but not to suicidal ideation (though this latter is controversial). It is interesting to note that it is suspected that correlation of low CSF 5HIAA and suicide is limited to unipolar depression, where the autoaggression hypothesis of depression is more likely to be valid than in bipolar disorder. However, Mann *et al.* (1989) have offered an alternative hypothesis that a decreased CSF 5-HIAA level is already associated with bipolar disorder, and any further decrease which may be associated with suicidal behaviour is less easily demonstrated.

5. Is low CSF 5-HIAA genetic or environmental in origin?

While the familial nature of the marker and data from twins (Sedvall *et al.* 1980 a,b, 1984: higher concordance for CSF 5-HIAA in monozygotic than dizygotic twins) may support a genetic basis, findings in animals suggest that it may result from learned helplessness situations (Anisman *et al.*, 1980) or prolonged social isolation (Valzelli, 1981). Psychological processes do not occur in a biological vacuum and the marker may well be acquired.

6. How does low serotonin turnover interact with other factors in depression and suicide?

Asberg *et al.* (1986b) hypothesized that the marker may represent a vulnerability to depression, suicide, and external aggression. It may manifest in a suicide attempt only when significant adverse events occur or when perception of the situation is distorted by depression (Figure 11). Previous adverse events (e.g., early parental loss) may facilitate a more negative interpretation of the adverse events while factors like social support may contribute to ameliorating the effects of adverse events and depression. Thus, the authors note, we may be moving towards a psychobiology of suicide.

Mann *et al.* (1989) have hypothesized that neurotransmitter systems other than serotonergic probably determine whether the aggression is directed inwards (suicide) or outwards.

Carrot *et al.* (1981) opined that the Dexamethasone Suppression Test identifies a group of suicidal subjects different from that identified by low CSF 5-HIAA. This needs further study as Traskamn *et al.* (1980) found high levels of cortisol in the same depressed patients in whom low 5-HIAA was found.

## TREATMENT IMPLICATIONS

The correlation between low CSF 5-HIAA and suicidal behaviour leads logically to the implication that drugs that enhance serotonergic activity should be evaluated as a specific treatment for it.

Montgomery and Montgomery (1982) found that zimelidine , a selective serotonin reuptake inhibitor decreases suicidal ideas at the beginning of treatment. However, recent case reports associated treatment with fluoxetine with increase in suicidal ideation. Lopez-Ibor *et al.* (1989) found (nonsignificant) trends for patients with suicide attempts, greater self-aggressivity, and lower CSF 5-HIAA levels to improve with treatment with 5-hydroxytrytophan (a serotonin precursor).

Morand *et al.* (1983) and Volavka *et al.* (1990) found trytophan to diminish aggressive behaviours in chronic schizophrenics. It has been suggested that drugs like carbamazepine, lithium and propranolol, which are effective in some cases of aggression, have important interactions with serotonergic systems and should be evaluated in impulsive suicidal behaviour (Editorial, Lancet, 1987).

Mann *et al.* (1989) have suggested that antidepressants may be effective in non-depressive suicidal behaviours as well due to effects on the 5-$HT_2$ and B receptors opposite to those found in the brains of suicide victims.

## CONCLUSIONS

Markers of central serotonergic activity, especially CSF 5-HIAA, may be one of the strongest predictors of suicidal behaviour. Sidney-Jones *et al.* (1990) found that while elderly suicide attempters had significantly lower CSF 5-HIAA levels than non-attempters, the Buss-Durkee Hostility Inventory (measure of aggression and impulsivity), the Brief Psychiatric Rating Scale, the Hamilton Depressive Rating Scale and the Recent Life Changes Questionnaire failed to distinguish the two groups. However, the predictive ability of these markers needs to be evaluated by prospective studies. The author is at pains to emphasize that this review focussing on one important biological variable should not be viewed as an oversimplified , reductionist etiology of suicide. Psychological processes not only interact with biological factors but have biological correlates and results as well: the brain is the seat of the mind. It cannot be assumed (as in much of biological psychiatry) that these markers are the biological cause rather than the biological substrate of the psychological processes underlying suicidal behaviour: psychological processes do not occur in a biological vacuum. For a unified psychobiological theory of suicide it is suggested that relevant psychological and biological variables be studied in the same group of patients to determine their interrelationships, eventually in prospective studies which would also evaluate their relative predictive ability. Some of the various drugs which interact with serotonergic systems may emerge as a treatment for suicidal behaviour as such in a defined subgroup of patients.

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