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TILAK VENKOBA RAO ORATION

PSYCHOBIOLOGY OF DEPRESSION*

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Introduction

I am grateful to you all, the Chairman and members of awards committee of Indian Psychiatric Society for conferring upon me the prestigious “Tilak Venkoba Rao Oration” Award for 1987. As you all know, this oration is instituted in memory of late Tilak Venkoba Rao, to encourage young psychiatrist to undertake research work in the field of biological psychiatry. My inspiration for research in psychiatry came from Prof. V. N. Bagadia during my postgraduate training in psychiatry, at the department of psychiatry, Seth G. S. Medical College and K.E.M. Hospital. Much work on depression had already been done at this department. (Bagadia et al 1973a, 1973b, 1973c). My work on depression was carried out at this department, W.H.O. Collaborating Centre for Psychopharmacology in India and at other centres where I am still working i.e. 1) Municipal General Hospital, Rajawadi, Ghatkopar, Bombay, 2) Pragati Hospital, Mulund and 3) Private Clinic.

Depression is universal; its clinical features were described in ancient Indian literature by Sudraka, a renowned playwright of the 2nd century B.C. (Kale 1972). A disease of antiquity, depression is an illness with a long ancestry. Depressive illness figures fairly prominently in the sacred writings of India, its mythologies; literature, the twin epics Ramayana and Mahabharata; its folklore and its ancient medical monographs and compendium. The hero of Ramayana, Rama suffers from the first episode in his fifteenth year. Rama's father suffers thrice from depression and the third attack proves fatal. He dies of grief. Rama's grand-father King Aja was a victim of the same illness for several years following the death of his wife and he starved himself to death. This again highlights the heritability of depression and the possibility of suicide and death from acute depression. Depression striking Arjuna in the Mahabharata epic was relieved by Lord Krishna’s admonition and counselling in Bhagavad Gita (Venkoba Rao 1984).

Depression is seen in people of all lands and every culture, affecting both the sexes, sparing neither the high nor the low, tormenting all ages, forcing the exit of some through self-destruction and steadfastly maintaining its core clinical features down the centuries.

The term “Depression” is so commonly used in every-day transactions that it fails to convince a layman and a busy medical practitioner that “Depression” could be a clinical entity. The depth and intensity of
depression is not usually recognised by the relatives or by the physicians. It is one of the most agonising illnesses and its real intensity is experienced only by the sufferer. In recent years considerable research has been done in cases of depression. Though the aetiology has not been unearthed as yet, the outcome of treatment of depression has been most rewarding.

The period prevalence of all forms of depression has been estimated to be around 3 per cent per annum, denoting that there are about 100 million people in the world each year, who develop clinically diagnosable and treatable depression (Lehman 1971). Watt (1966) drew the iceberg model of the depressive illness with the visible portion comprising 15-20 per 1000. The largest invisible portion was formed by nearly 150 depressives per 1000 population. Though depression is an ubiquitous dysphoric experience, few seem to consult doctors and still fewer the psychiatrist. Davies and Blashki (1974) found that out of 85 depressives who consulted general practitioners, only 2 were referred to the psychiatrists.

Inspite of this, the volume of depressives, consulting psychiatrist is very large and today I shall be concentrating on the following areas of depressive illness: 1) Epidemiology 2) Clinical profile of depression 3) Life events and depression 4) ABO Blood groups in bipolar and unipolar affective disorders 5) Tricyclic antidepressants 6) Tetracyclic antidepressant 7) Multi-centric collaborative study 8) Pattern of antidepressant use in India. These are the areas in which I have personally worked and therefore merit greater attention.

1. EPIDEMIOLOGY

Earlier notion of the uncommonness of depression in India were advanced by some British Psychiatrist, appointed to the mental asylums in the country. The data concerning occurrence of depression at all levels of clinical encounters; in mental hospitals; in general hospitals; in psychiatric clinics; in general medical practice and in the community, are now available. The prevalence of the illness in the general population in the different parts of the country varies from 1.27 to 49.1 per 1000 population (Kapoor and Singh 1983).

In view of the lack of reliable estimates in the general population, it may be useful to look at the incidence figures for depression within the hospital population. Admittedly, there are several factors which determine whether a person will seek treatment or not, but assuming that these factors will operate equally for all psychiatric illnesses in a given population, we can get an estimate of the relative frequency of depressive illness as compared to other psychiatric disorders. The relative occurrence of depression in Bombay is as follows: General teaching hospital, 9% of total attendance; a private non-teaching hospital patronized by middle class, 28% of total attendance and a private practice, largely consisting of upper-middle and upper class patients, 37% of total attendance (Bagadia et al. 1979a). From the various reports (Venkoba Rao 1984), it appears that the occurrence of the depressive illness is four to five times more in the northern eastern India than the western and southern India.

The incidence of depression from private clinics, is reported to be higher than that from teaching general hospital (Table 1). When figures from private clinics are compared with other studies from north India, incidence is nearly the same. In Bombay, general teaching hospitals usually cater for
lower socio-economic group. The patients who can afford to pay, will preferably take treatment in private clinic for all illnesses, including the psychiatric illnesses. Also, taking treatment in general teaching hospitals by such affording people is socially disapproved. Depression is more common in higher socio-economic group (Neki and Kapoor 1963, Slater and Roth 1969). Thus the incidence of depression in western India is similar to that reported from eastern and northern India. It will be interesting to compare the findings of the incidence of depression from teaching general hospitals and private clinics from other parts of India. The diagnostic criteria for depression have been changing from time to time and may account for some of the differences seen among studies. Yet the impression remains that the endogenous/psychotic variety of depression is more in the North and less in the South with intermediate figures in the West.

2) **CLINICAL PROFILE OF DEPRESSION**

Hundred consecutive new cases diagnosed as suffering from depression of non-organic cause according to I.C.D.-9 (WHO 1978) were studied in detail in a prospective way at Pragati Hospital, Mulund, Bombay (Gada 1982). The presence or absence of a particular symptom was rated on Hamilton Psychiatric Rating Scale for Depression (Hamilton 1960).

The symptoms reported in four other studies (two Indian and two British) of depressed patients were compared with the findings of the present study. Out of two Indian studies, one was from North India (Teja et al. 1971) and included 100 cases, other was from South India (Venkoba Rao 1966) and included 30 cases. The other two British studies, were from Newcastle Upon-Tyne. Kiloh and Garside's (1963) study included 143 depressive patients and Carney et al. (1965) included 116 depressed patients.

The percentage of symptoms in the present study were compared statistically with those found in other four studies.

**Chief complaints:**

66% of cases presented with physical symptoms only, whereas only 5% of cases had psychological symptoms. 29% cases had both physical and psychological symptoms (Gada 1980a). More often than not, psychiatric patients in our culture complain mainly of physical symptoms. Several investigators from different parts of our country (Venkoba Rao 1966, Ansari 1969,
Bhattacharya and Vyas 1969, Teja et al. 1971, Bagadia et al. 1973) have substantiated this observation. Similar preponderance of physical symptoms have been observed among depressed patients from Africa (Lambo 1956), from middle east countries (Bazzoni 1970), from Bangladesh (Rahman 1970) and from China (Tseng 1975).

In psychiatric illnesses, important determinants of the choice of symptoms, include those symptoms which are assigned the status of an illness by the group to which the patient belongs, as well as the expectancy on the part of patient of what local doctors consider as an illness. The chances of purely psychological symptoms being dismissed as not of much consequence, are high in India. The Indian patient, therefore, uses the medium of the body more often for expressing inner tensions, and his depressive affect gets translated into the language of the body. The differences between the high incidence of hysterical symptoms among Indian, and of open anxiety among British soldiers, under similar situations of stress during last world war, support the same view (Williams 1950).

Symptom Profile:

Table 2 shows the frequency of symptoms of depression seen in 100 cases.

The present study reveals that 15 of the 21 symptoms of depression on Hamilton Psychiatric Rating Scale for Depression were present in more than 60% of the cases. Depressed mood and somatic anxiety were present in all the 100 cases, insomnia in 94%, guilt feelings in 27%, depersonalisation and derealisation in 14%, obsession and compulsive symptoms in 6% and paranoid symptoms in 4%.

Statistical interpretation of the comparison of the present findings with those of the other four studies are given in Table 3.

A comparison of my study with that of Teja et al. from North India, indicates that somatic anxiety was significantly greater whereas guilt feelings, late insomnia, work and activities, retardation and paranoid symptoms were significantly less in my study. A comparison with Venkoba Rao's study from South India indicates that depressed mood, somatic anxiety, and hypochondriasis were significantly more, whereas suicidal tendency and diurnal variation were significantly less in my study.

All except four symptoms were significantly more frequent in my study as
Table 3
Statistical significant differences in various symptoms compared with present study

| Symptoms                  | Present study v/s Teja et al | Present study v/s Venkoba Rao | Present study v/s Kiloh & Garside | Present study v/s Carney et al |
|---------------------------|------------------------------|-------------------------------|----------------------------------|--------------------------------|
| Depressed mood            | n.s                          | 0.01                          | 0.001                            | 0.001                          |
| Feelings of guilt         | 0.01                         | n.s                           | n.s                              | 0.001                          |
| Suicidal tendency         | n.s                          | 0.01                          | 0.01                             | 0.001                          |
| Insomnia—early            | 0.05                         | —                             | 0.001                            | 0.001                          |
| Insomnia—middle           | 0.05                         | —                             | —                                | —                              |
| Insomnia—late             | 0.001                        | n.s                           | 0.001                            | n.s                            |
| Work and activities       | 0.001                        | —                             | —                                | —                              |
| Retardation               | 0.001                        | n.s                           | n.s                              | 0.05                           |
| Agitation                 | n.s                          | n.s                           | 0.001                            | —                              |
| Anxiety psychic           | 0.05                         | n.s                           | 0.001                            | 0.001                          |
| Somatic symptoms          | 0.01                         | 0.01                          | —                                | 0.001                          |
| Genital symptoms          | n.s                          | n.s                           | —                                | —                              |
| Hypochondriasis           | n.s                          | 0.001                         | 0.001                            | 0.001                          |
| Loss of weight            |                              |                               |                                  |                                |
| Diurnal variation         | n.s                          | 0.05                          | 0.001                            | 0.001                          |
| Depersonalisation & Derealisation | n.s | n.s | — | — |
| Paranoid symptoms         | 0.05                         | —                             | 0.001                            | 0.05                           |
| Obsessional & Compulsive Symptoms | n.s | n.s | 0.001 | — |

n.s = not significant

Compared to that by Kiloh and Garside, but paranoid and obsessional symptoms were significantly less in the present study. Guilt feelings and retardation showed no difference between the two studies. In my study, all items were significantly more frequent as compared to that of Carney et al. except for guilt feelings and paranoid symptoms, which were significantly less.

In my study, guilt feelings were found in only 27% of the cases. The relatively less frequent occurrence of guilt feelings among Eastern patients has been commented on by a number of workers. The guilt feelings reported by Indian patients are generally of an impersonal character—present suffering is usually attributed to possible bad deeds of previous life, a consequence of one's 'Karma'. Individualised guilt is experienced less often and that too by the more educated patients. Conformity is highly valued in the Indian social system. An average Indian views his life role more as part of a social system than as belonging to a unique individual. The dictates of the superego continue to be dependent on the external sources to a fairly large extent. In contrast, the assumption of a greater degree of individual responsibility and independent role playing by the average Westerner is likely to foster a sense of guilt, emanating from one's own realisation of self-failure.

Obsessional and paranoid features are encountered to a significantly less extent in
Indian as compared to Western depressives. Since rituals are a well accepted day to day practice of the Indian socio-religious system, such features are not likely to be considered as hampering symptoms by the patient or by his relatives. In fact, in some cultures, rituals are encouraged, even though they may be taxing to the individuals. The relatively more competitive existence of the Western individual probably tend to foster the development of suspicious paranoid attitudes and this may possibly explain the greater frequency of this symptom among British depressives. Orelli (1952) in Switzerland, studying changes in the content of depressive delusions during period 1878-1951, found a significant shift away from delusions and feeling of guilt towards feelings of personal inadequacy, paranoid and hypochondriacal symptoms.

(3) LIFE EVENTS AND DEPRESSION

Life without stress cannot be imagined. Psychological stresses form an inseparable part of the life and upto a degree may be essential for adequate personality development. However when these stresses become too severe or too numerous, they may affect the psychic equilibrium, producing maladaptive patterns and possibly mental disorders. The notion that major stressful events in life can give rise to mental illness is prevalent since antiquity. But scientific investigations in this area have been carried out only in the last few decades. Life event research is one of the ways of systematically studying the relationship between stress and illness.

The basic method in the life event research is determination of significant events in the specific period of a person's life and their correlation with subsequent illness, physical and/or psychological. Life event research is based on the underlying presumption that significant events require some readjustment in life and produce significant upsetting. An accumulation of these events in succession produce a non-specific vulnerability for the development or precipitation of physical and psychiatric disorders.

Hundred patients, 64 males, 36 females, suffering from Major Depressive Disorder (M.D.D) at a private clinic comprised the sample for the study. The diagnostic work up of the cases was based on R.D.C. as proposed by Spitzer et al. in 1972. 100 normals matched for age, sex, marital and economic status who had never consulted before for psychiatric advice served as control. Both these groups were administered life events schedule by the author, for finding out events experienced in the previous 12 months. To increase the reliability, 12 months recall period was used, as recall of events in recent time periods is better than remote events (Jenkins et al. 1979). Semistructured interview was used and subjects were asked to indicate only the occurrence of events and not its frequency. The period of 12 months was divided into 0 to < 1 month, 1 to < 3 months, 3 to < 6 months and 6 to 12 months. For patients, 12 months period was before the inception of M.D.D. and for the controls it was 12 months period before the date of the interview. Life events schedule was devised by the author to suit the Indian population after modifying the international life events of Holmes and Rahe (1967), of Paykel et al. (1971), and of Venkoba Rao and Nammalvar (1976). At the time this study was conducted Dr. Gurmeet Singh's standardized PSLE scale (Singh et al. 1981) was not available and was probably under investigation. My scale contained 72 items, Paykel and co-workers' (1969, 1975) following comparison
methods between events experienced by the patients and controls were used:

1. Total number and mean number of events experienced.

2. Comparison of frequency of occurrence of each event between patients and controls.

3. Classification of events into categories like:
   a) Exit and entrance from social field.
   b) Desirable and undesirable, in terms of shared value of society.
   c) Areas of activity like health, employment, family, marital and legal.

| Table 4 | Average number of events |
|---------|--------------------------|
|         | 0 to < 1 | 1 to < 3 | 3 to < 6 | 6 to 12 |
|         | month   | months  | months  | months |
| No.    | Ave.    | No. Ave.| No. Ave.| No. Ave.|
| Control| 15      | 15      | 28      | 41      | 13.6    | 73      | 12.1    |
| Patients| 37      | 37*     | 48      | 24*     | 69      | 23*     | 101     | 16.8    |

* P < 0.01
** P < 0.001

In this study it was observed that depressed patients reported significantly more number of life events than normals. Also there was clustering of average number of events particularly one month before the inception of depression.

Saxena and Mohan (1982) have discussed excellently the methodological issues about life events research. In the present study, many of the issues were taken care of even before Saxena and Mohan’s guideline for life-events research were available.

Venkoba Rao and Nammalvar (1976), Prakash et al. (1980), Chatterjee et al. (1981), Gupta et al. (1981) have reported association between life events and depression. Brown (1972) has advanced the concept of “brought forward time” which is derived from elaborate calculations. Essentially it supposes that the illness was any way destined to begin in future and stressful events bring this onset nearer.

Considerable caution must be exercised in assigning causal relationship between events and illness. It should not be forgotten that life events constitute only one of several factors in the causation of illness.

(4) ABO BLOOD GROUPS IN BIPOLAR AND UNIPOLAR AFFECTIVE DISORDERS:

One of the methods of studying the association between a psychiatric disorder and established genetic traits has been the determination of ABO blood groups.

A number of studies have been reported on the association between affective disorders and ABO blood types. Some workers (Parker et al. 1961; Masters 1967; Mendlewicz et al. 1974) have reported significantly greater incidence of the type O blood group in manic-depressive group. Others (Tenna and Winokur 1968; Flemenbaum and Larson 1976) have not confirmed the same. All these workers have considered manic-depressive illness as one single entity. The unity of manic-depressive illness as defined by Kraeplin (1921) has been questioned by several investigators (Leonard 1966; Perris 1966) who have presented clinical and genetic evidence that the disease is heterogenous and consists of two distinct types, unipolar and bipolar affective disorders. The overrepresentation of any one of the two subcategories may...
### Table 5
Type of life events

| Type                  | 0 - <1 month | 0 - <3 months | 0 - <6 months | 0 - <12 months |
|-----------------------|--------------|---------------|---------------|---------------|
|                       | Nor. N = 15  | Dep. N = 37   | Nor. N = 43   | Dep. N = 85   | Nor. N = 154  | Dep. N = 255 |
| Bereavement           |              |               |               |               |               |              |
| Health                |              |               |               |               |               |              |
| Financial             |              |               |               |               |               |              |
| Family/relatives      |              |               |               |               |               |              |
| Occupation            |              |               |               |               |               |              |
| Education             |              |               |               |               |               |              |
| Legal                 |              |               |               |               |               |              |
| Migration             |              |               |               |               |               |              |
| Others                |              |               |               |               |               |              |

* p < 0.01  ** p < 0.001

### Table 6
Individual events

| Individual events                | 0 - 1 month | 0 - 3 months | 0 - 6 months | 0 - 12 months |
|----------------------------------|-------------|--------------|--------------|--------------|
|                                  | Nor. N = 15 | Dep. N = 37  | Nor. N = 43  | Dep. N = 85  | Nor. N = 154 | Dep. N = 255 |
| 1 Serious Personal Physical Illness | 0           | 2*           | 0            | 4**          | 1            | 7*           | 1            | 9*          |
| 2 Minor Personal Physical Illness | 1           | 2            | 1            | 3            | 2            | 8            | 4            | 12          |
| 4 Academic Failure               | 0           | 1            | 1            | 2            | 2            | 4            | 3            | 8           |
| 12 Law Suits                      | 0           | 0            | 1            | 2            | 1            | 2            | 3            | 5           |
| 13 Death of Spouse               | 0           | 2*           | 0            | 3*           | 0            | 5**          | 1            | 7*          |
| 15 Serious Illness of Spouse     | 0           | 2*           | 0            | 4**          | 1            | 5            | 3            | 8           |
| 16 Minor Illness of Spouse       | 0           | 1            | 1            | 2            | 3            | 4            | 5            | 7           |
| 17 Serious Arguments with Spouse | 0           | 1            | 1            | 3            | 2            | 6            | 4            | 9           |
| 29 Death of Child                | 0           | 2*           | 1            | 4            | 2            | 7            | 3            | 10          |
| 30 Serious Illness of Child      | 0           | 2*           | 0            | 3            | 1            | 5            | 3            | 8           |
| 31 Minor Illness of Child        | 1           | 1            | 2            | 2            | 4            | 4            | 7            | 6           |
| 33 Serious Arguments with Child  | 1           | 2            | 3            | 4            | 6            | 8            | 10           | 13          |
| 40 Death of parents              | 1           | 2            | 1            | 4            | 2            | 5            | 3            | 7           |
give rise to erroneous findings and true relationship may disappear. This may account for the inconsistent findings of the investigators.

In four studies (Shapiro et al. 1977, Beckman et al. 1978, Riniers et al. 1979, Singh et al. 1979) and one conducted by the author (Gada 1986) the dichotomy of manic-depressive illness (i.e. division into unipolar and bipolar affective disorders) has been realised.

As part of a clinical study of primary affective disorders, it was decided to investigate the ABO blood groups of all probands attending municipal general hospital, Rajawadi, Ghatkopar, Bombay. In addition to a diagnosis of affective psychosis according to the International Classification of Disease (9th revision), all subjects were required to fulfill the R.D.C. as proposed by Feighner et al. (1972) for inclusion in the present study. No one was admitted to the study who had evidence of another pre-existing psychiatric illness. The designation of patients as unipolar or bipolar was made according to the following criteria. a) Patients with at least one definitely manic episode at the time of index admission or in the past, with or without a definite depressive episode, were diagnosed as bipolar. b) For diagnosis of unipolar illness the criterion of at least two definite depressive episodes, as proposed by Mandlewicz and Rainer (1968) and also Johnson et al. (1977) was used. c) In addition any subject with a history of mania, in any family member, was excluded from the unipolar group. d) Patients with only one episode of depression or a mixed picture, although fulfilling the criteria for primary affective disorders, were considered of uncertain polarity and therefore excluded from the study.

Blood group frequencies for the general population were calculated from the records of the subjects registered and tested at the blood bank of Municipal General Hospital, Rajawadi, Ghatkopar.

Comparison of the bipolar group with normal controls: \( \chi^2 = 11.372, \) d.f.
Table 8
Distribution of ABO Blood Groups in Bipolar and Unipolar patients and Normal Controls

| ABO | Normal controls (N = 56) | Bipolar patients (N = 56) | Unipolar patients (N = 44) | Total (Bipolar + Unipolar) (N = 100) |
|-----|--------------------------|---------------------------|---------------------------|-------------------------------------|
|     | Percentage               | No. Percentage            | No. Percentage            | No. Percentage                      |
| O   | 36.0                     | 29 51.8                   | 16 36.4                   | 45 43.0                             |
| A   | 25.0                     | 9 16.1                    | 9 20.4                    | 18 18.0                             |
| B   | 31.0                     | 15 26.8                   | 15 34.1                   | 30 30.0                             |
| AB  | 8.0                      | 3 5.3                     | 4 9.1                     | 7 7.0                               |

= 3 \( p < 0.01 \) and with unipolar group \( (x^2 = 11.510, d.f. = 3, p < 0.01) \) on total distribution of blood groups showed a significant difference suggesting that the bipolar group was different from the normals and unipolar group. A closer examination of the individual blood types revealed that the bipolar group had significantly higher percentage of cases with blood group O than either normal controls \( (X^2 = 4.100, d.f. = 1, p < 0.05) \) or unipolar group \( (X^2 = 4.133, d.f. = 1, p < 0.05) \). No significant difference was observed in other blood groups.

In the case of the unipolar group no significant difference were found when compared to controls for total distribution of blood groups or any of the blood groups.

When manic-depressive illness is divided into unipolar and bipolar affective disorders, the consistent finding emerges, i.e. bipolar affective group has significantly higher frequency of blood group O in comparison to normal controls and unipolar affective group. In both the Indian studies unipolar affective patients, were not different from normal controls as far as ABO blood group was concerned.

It would be reasonable to postulate that blood group factors represent one among other relevant genetic variables. The contribution of blood group variation in disease susceptibility is justifiable to the assertion that blood group association imply the hereditary aspect in the aetiology of a disease.

Pharmacotherapy of Depression

The first drug shown to be therapeutically effective in the treatment of depression was imipramine. Its possible anti-depressive properties were recognised as early as 1956 (Kuhn 1957) and soon further substantiated independently in Europe (Kielholz and Battergay 1958) and North America (Lehman et al. 1958). In spite of its great practical implications, however, it was not until 1959 that the first controlled trial definitely confirmed the anti-depressant effects of imipramine (Ball and Kiloh 1959).

Since then, a rather large number of imipramine like tricyclic and tetracyclic anti-depressants (TTA) have been synthesized and employed clinically (Ban 1974). Originally TTA were a structurally homogenous group of tricyclic anti-depressants with the common pharmacological property of blocking the reuptake of biogenic amines, primarily norepinephrine and serotonin, across the presynaptic neuronal cell membrane. Today they are a structurally heterogeneous group of drugs, with at least ten different tricyclic and ten different non-tricyclic
structures, possibly with a common final path in affecting noradrenergic transmission by down-regulation of beta-receptors in postsynaptic neurons (Creese and Sibley 1981). Although there is no evidence for different therapeutic actions, these drugs differ in their adverse effects, such as those associated with their hypotensive, sedative and anti-cholinergic properties. These effects seem to be linked to affinities for alpha1 adrenergic receptor, histamine1 receptors and acetylcholine muscarinic receptors, respectively (Richelson 1979). Furthermore, by the demonstration of a decrease in the number of imipramine binding sites, the possibility of a biological marker for therapeutic responsiveness to TTA has become distinct possibility (Briley et al. 1982).

(5) TRICYCLIC ANTI-DEPRESSANTS:

A six week double-blind controlled comparative trial of amoxapine and imipramine was carried out in 66 depressed patients of both sexes attending the outpatient department of a general teaching hospital (Bagadia 1979b). Physical examination and psychiatric evaluations (Hamilton Psychiatric Rating Scale for Depression, Beck Depression Inventory and Clinical Global Impression Scale) were applied pretreatment and at weekly intervals for the entire duration of the trial (six weeks).

Forty-eight patients completed the study of 6 weeks. Results are as follows: by the end of second week there was good response in 25 per cent of cases. At the end of fourth week response was excellent in 25 per cent and good in another 52 per cent of the cases. By the end of sixth week 91.6 per cent had improved (excellent response in 60.4 per cent and good in 31.2 per cent). In endogenous depression 96.1 per cent of the cases had shown good to excellent response, where as in neurotic depression 13.6 per cent had not improved. The side effects consisting mainly of anti-cholinergic (dry mouth, constipation, delayed urine flow) and neurological (giddiness, tremor) symptoms, were mild, were tolerated by the patients on reassurance and acceptable to the physicians.

(6) TETRACYCLIC ANTI-DEPRESSANT (MAPROTLINE)

A four week, double blind comparative clinical study with 72 depressed psychiatric patients, was carried out, in which patients were randomly assigned to low or high dosage schedule, in a single daily dose given at bed time. Thus, patients of the low group were given maprotiline in the dosage of 37.5 mg. daily for three days and 75 mg. daily subsequently, while patients of the high dose group were administered a dosage of 75 mg. daily for three days and a dose of 150 mg. daily until the end of the 28 days treatment period.

Assessments were based on clinical interviews and the completion of three psychiatric rating scales i.e. Clinical Global Impression Schedule, Hamilton Psychiatric Rating Scale for Depression (HAM-D) and Rating Scale for Side Effects (RSSE) before, the 14th, 28th, 42nd and 84th day of drug administration.

Fifty-nine patients completed 4 weeks of study and 49 patients completed total period of 12 weeks. Of 59 cases, 8 (13.6%) were of moderate severity and 51 (86.4%) had severe depression.

Scores of the Global Improvement did not differ statistically in the low and high dosage groups after two and four weeks of
treatment although the scores did show significant improvement in each group. By separating patients into three groups, (A) improved, (B) unchanged and (C) worsened, 84.4% of the patients in the low and 85.2% of the patients in the high dosage group were judged to be improved at the end of four weeks treatment.

Table 10 shows: there was statistically significant improvement in total scores, all five factor scores and 15 of the 17 item scores on HAM-D in the total population after two weeks of treatment; and in one more item score by the end of the fourth week. Analysis of covariance did not reveal any statistically significant difference between the two groups for any item, factor or total score.

The side effects observed (on RSSE) were drowsiness, constipation, tremor, orthostatic symptoms, dryness of mouth, perspiration and micturition difficulties. Analysis of covariance indicated that high dose patients had a significantly greater increase (worsening) in total scores and in the item scores of constipation and orthostatic symptoms than low dose patients.

(7) DOSE EFFECTS OF ANTI-DEPRESSANT MEDICATION IN DIFFERENT POPULATIONS - A WORLD HEALTH ORGANISATION COLLABORATIVE STUDY:

Patients included in the study were 370 adults (WHO 1986). There were 31 patients in Basel, 72 in Bombay, 68 in Cali, 54 in Lucknow, 35 in Nagasaki, 41 in Nashville and 69 in Sapporo, 324 patients were available for the final analysis (in 30 patients no second assessment was available and 16 patients were excluded prior to completing 4 days of active treatment) with adequate representation from each centres.

The clinical study consisted of three distinct phases which were conducted on the
basis of an identical protocol at all centres. The first phase of the study followed a conventional, design in which patients were randomly assigned to one of two, a low and a high, dosage regimes (day 0) and treated on the basis of a fixed changing dosage schedule in a double-blind manner over a period of 28 days (days 1-28). Patients of the low dose group were given 37.5 mg. daily for three days and 75 mg. daily subsequently, while patients of the high dose group were administered a dosage of 75 mg. daily for three days and a dose of 150 mg. daily until the end of the 28 days treatment period. Subsequently, during the second phase of the study, patients were treated on the basis of a flexible dosage regime in an open manner over a period of 14 days (days 29-42) with the same drug used during the first phase. By allowing for free adjustments of the dose, it was hoped that optimal therapeutic dose levels would be attained. Finally, during the third phase of the study patients were treated in a completely free and open manner, with drugs or other treatments, at the discretion of the attending psychiatrist for an additional period of 42 days (days 43-84).

The parameters of assessment were (1) Part 2 (symptom and signs) of WHO Schedule for Standardized Assessment of Depressive Disorders (WHO/SADD), (2) Hamilton Psychiatric Rating Scale for Depression (HAM-D), (3) Rating Scale for Side Effects (RSSE) and (4) Clinical Global Impression Scale (CGIS).

The salient findings were as follows:

1) Most patients selected for the treatment in this investigation showed a good response during the first 28 days.

2) No statistically significant difference was found between the response to treatment, as measured on HAM-D total score, the Clinical Global Impression of Severity and all the items of the HAM-D taken separately.

3) The response to treatment showed significant differences between centres.

Follow-up

There was an inverse relationship between Efficacy Index (EI) and rate of continuation for amitriptyline and imipramine patients, i.e. the greater the improvement (and the fewer the side effects) the more likely it was that there will be a continuation of treatment with these drugs. In this respect, patients who continued for 42 days did not differ from those who continued over the entire 84 day period. These findings also imply that patients who respond favourably to treatment are most likely to continue with the maintenance therapy.

Treatment Emergent Symptoms

The Rating Scale for Side Effects, consisting of 13 items, was used to record treatment emergent symptoms, i.e., manifestations with an onset during the course of treatment. Tremor and nausea/vomiting occurred statistically significantly more often in the high than in the low dose group.

8) PATTERN OF ANTIDEPRESSANT USE BY INDIAN PSYCHIATRISTS

A study by questionnaire was carried out at the W.H.O. Collaborating Centre for Psychopharmacology in India (Bombay) to ascertain prescribing patterns, choice of drugs, dosage, duration, side effects and concurrent use of other modalities of treatment by Indian Psychiatrists in depressed patients (Gada et al. 1984). The
results analysed, from the replies received, were as follows:

Imipramine and amitriptyline were the two most commonly used antidepressant drugs in India. More than 80% of Indian Psychiatrists use imipramine and amitriptyline as either first or second choice of antidepressant drugs. Three fourths of the psychiatrists use up to 150 mg per day as a therapeutic dose and up to 75 mg per day as maintenance dose. Two thirds use therapeutic dose for less than 3 months whereas half of the psychiatrists use a maintenance dose for less than 6 months. Ninety-seven percent of the Indian psychiatrists use electro-convulsive therapy and psychotherapy, concurrently with antidepressant drugs. Commonest side effects observed on Indian patients are dryness of mouth, constipation, and drowsiness. Commonest contraindication for use of the antidepressant drugs in India are glaucoma, enlarged prostate, recent myocardial infarction and other cardiac diseases.

In children, apart from its use in depression, antidepressant drugs are used in enuresis, hyperkinetic behaviour and school phobias.

The response of majority of Indian depressed patients to tricyclic and tetracyclic antidepressant drugs is good to excellent and usually occurs within two to six weeks. Tolerance to these drugs is also reportedly good.

All human beings are biological, psychological and sociological creatures. It is the interaction of all these factors that leads to an illness, more so as psychiatric illness. Depression is an illness with multifactorial aetiology. Interplay of psychosocial and biological factors i.e. psychobiological aspects, leads to depression. Life events by themselves or biological predisposition by itself will not produce the illness.

In the psychobiology of depression there are many more areas like genetic studies, twin studies, family studies indicating X-linkage, relation to colour-blindness. There are biochemical studies, indicators of vulnerability in the RBC enzyme systems, classification according to suppression or otherwise of dexamethasone (DST), treatment by electroconvulsive therapy, tryptophan and diet regulation, newer antidepressants like bicyclics etc., etc. These are areas in which as of date, I have not ventured but given the opportunities, I intend to continue research in this sphere which presently myriad openings for further investigations.

Radhakrishnan once remarked that "Science humbles its votary and it makes him realise how little he knows and how vast is the unknown". Extending the frontiers of knowledge, rather than solving the mystery heightens it. It will be appropriate to conclude this oration by these lines of Rabindranath Tagore:

This is my prayer to thee, my Lord—
Strike, Strike at the root of penury in my heart,
Give me the strength lightly to bear joys and sorrows,
Give me the strength to make my love fruitful in service,
Give me the strength never to disown the poor or bend my knees before insolent might,
Give me the strength to raise my mind high above daily trifles.
And give me the strength to surrender my strength to thy will with love.

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