DEPRESSION IN PATIENTS WITH EPILEPSY

by

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T O M Y P A R E N T S

ABSTRACT

Review of the literature suggests that depression is the most common psychiatric illness of epilepsy. Moreover, similar aetiological theories and pathogeneses have been forwarded regarding the 2 illnesses. However, there have been no studies into the precise phenomenology of the depression in the context of epilepsy, nor its treatment. In this thesis, the relevant literature is reviewed, followed by 3 studies.

The first part of the original research investigated the phenomenology of the depression in 66 people with epilepsy. Standardised rating scales were used for measuring aspects of mood and personality. The depression was both endogenous (37.9% or 42.4%, depending on the rating scale used) and non-endogenous. On all rating scales the depression was of moderate severity, and comparable with the degree of depression reported in studies of non-epileptic depressed populations. State anxiety, neuroticism and hostility (especially the intropunitive scores) were extremely high. The depression was accompanied by a feeling of being a burden to others (81.8% of patients) and suicidal ideation or attempts (51.5% of patients). Forty-three (65.2%) of patients had a past history of depression and had significantly higher depression scores. The patients had high Trait anxiety and 53 (80%) were classified as obsessoid. Thirty-four (52.3%) had a family history of psychiatric illness. Serum folic acid ($p<.05$) and red blood cell folic acid ($p<.001$) were significantly lower than that of a control population. Patients receiving phenobarbitone were significantly more depressed ($p<.05$), while those receiving carbamazepine were significantly less depressed ($p<.05$) and had lower Trait anxiety scores ($p<.05$) than those not on the drugs. Duration of epilepsy was significantly associated with the severity of the depression, as measured by the Beck Depression Inventory ($p<.05$): however, neither the type nor severity of depression were significantly associated with the type of epilepsy, site of a focal lesion nor seizure frequency. A significant relationship ($p<.05$) was found between patients who had complex partial seizures and a past history of depression; in addition, patients with complex partial seizures had significantly lower serum folic acid ($p<.05$) than did those with generalised epilepsy. A control population of age and sex matched epileptics with no psychiatric impairment had electroencephalograms (EEG); no significant differences in EEG abnormalities between the patient and control groups emerged.

The second study investigated the clinical usefulness of the Dexamethasone Suppression Test (DST) in identifying a subgroup of depressed epileptics. It is suggested that the DST is of no practical value as a biological marker in this context. What emerged, however, was that a control group of non-depressed epileptic patients on monotherapy with sodium valproate (VPA) differed significantly from a group of depressed epileptics and a control group of non-depressed epileptics, both on anticonvulsants which induce hepatic enzymes ($p < .05$). In addition, the post DST serum cortisol levels of the patients on VPA were significantly lower than those of the other 2 groups ($p < .01$).

The third study was a double blind antidepressant trial using amitriptyline, nomifensine and placebo. In all treatment groups the depression scores fell significantly over 6 weeks ($p < .0001$), but no significances between the 3 trial drugs emerged. No significant association was found between serum nomifensine levels and clinical response at 6 weeks, but significant and negative correlations between serum amitriptyline levels and response were found ($p < .05$). No significant differences between serum anticonvulsant levels of patients on amitriptyline, nomifensine or placebo emerged. No significant changes in seizure frequency occurred during the trial. When the active agents were doubled in non-responders, nomifensine was significantly superior to amitriptyline ($p < .05$). Doubling the dose of amitriptyline increased serum levels at both 09.00 hrs ($p < .001$) and 13.00 hrs ($p < .01$), while doubling the dose of nomifensine significantly increased the serum levels at 09.00 hrs ($p < .05$).

The results of these experiments, in the context of the literature, suggest that: 1) The depression in people with epilepsy may well represent the outcome of multiple factors in genetically predisposed individuals. The possibility that a subgroup with a more biological loading is raised; 2) The DST is not helpful in distinguishing a subgroup of epileptics with affective illness. Non-suppression, however, was associated with VPA treatment; 3) Antidepressant medications might not be indicated in the initial management of depressed epileptics. Should antidepressants be used, there is a suggestion that drugs which do not lower the seizure threshold may be more efficacious, and safer.

The limitations of the present studies and some suggested directions for future research concerning the interplay of epilepsy and affective disorders are discussed.

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GLOSSARY OF ABBREVIATIONS

ACh	Acetylcholine
ACTH	Adrenocorticotropic hormone
ANOVA	Analysis of Variance
A-State	State anxiety
A-Trait	Trait anxiety
BDI	Beck Depression Inventory
BP	Blood pressure
CAT	Computerised axial tomography
CBZ	Carbamazepine
CCEI	Crown-Crisp Experiential Index
CL	Clonazepam
CNS	Central Nervous system
COMT	Catechol-o-methyltransferase
cps	Cycles per second
CSF	Cerebro spinal fluid
CSM	Committee on the Safety of Medicines
Cyclic Amp	Cyclic adenosine mono phosphate
DA	Dopamine
DH	Dehydrogenase
dl	Decilitre
DPH	Phenytoin (Diphenylhydantoin)
DSM III	Diagnostic and Statistical Manual of Mental Disorders (3rd edition), American Psychiatric Association
DST	Dexamethasone Suppression Test
ECT	Electro convulsive therapy
EEG	Electroencephalogram
EMIT	Enzyme Multiplied Immuno Assay Technique
EPI	Eysenck Personality Inventory
E (from EPI)	Extraversion
N (from EPI)	Neuroticism
ETH	Ethosuximide
FA	Folic acid
GABA	Gamma amino butyric acid
GH	Growth hormone
HDRS	Hamilton Depression Rating Scale
HDHQ	Hostility and Direction of Hostility Questionnaire
HDHQ subscales	
AH	Urge to act out hostility
CO	Criticism of others

PH	Paranoid hostility
SC	Self criticism
G	Guilt
5HIAA	5-hydroxy indole acetic acid
5HT	5-hydroxy tryptamine (serotonin)
5HTP	5-hydroxytryptophan
HIST	Histamine
HOQ	Hysteroid/Obsessoid Questionnaire
HPA	Hypothalamic-pituitary-adrenal
HVA	Homovanillic acid
IQ	Intelligence quotient
L/l	Litre
LEMs	Lateral eye movements
L-5-HTP	L-5-hydroxytryptophan
LH	Luteinising hormone
LPD	Levine-Pilowsy Depression Questionnaire
LPD-D Score	LPD depression score
LPD E-R Score	LPD endo-reactive score
MAO	Monoamine oxidase
MAOI	Monoamine oxidase inhibitor
mg	Milligram
MHPG	3-methoxy-4-hydroxy phenethyleneglycol
MHQ	Middlesex Hospital Questionnaire
ml	Millilitre
MMPI	Minnesota Multiphasic Personality Inventory
MPI	Maudsley Personality Inventory
NA	Noradrenaline
ng	Nanogram
NHQS	National Hospital, Queen Square
nm	Nanomol
OH	Hydroxy
PB	Phenobarbitone
PR	Primidone
PRL	Prolactin
PSE	Present State Examination
rbc	Red blood cell
RDC	Research Diagnostic Criteria
rpm	Revolutions per minute

S	Sulthiame
SD	Standard deviation
SHBG	Sex hormone binding globulin
SMR	Standard mortality ratio
STAI	State-Trait Anxiety Inventory
tid	Three times a day
TCA	Tricyclic antidepressant
TLE	Temporal lobe epilepsy
TRH	Thyrotrophin-releasing hormone
VEPs	Visual evoked responses
VMA	Vanillyl mandelic acid
VPA	Valproic acid (sodium valproate)
WAIS	Wechsler Adult Intelligence Scale
$>$	More than
$<$	Less than
χ^2	Chi^2
μ	Micro

INTRODUCTION

"The good physician is concerned not only with turbulent brain waves but with disturbed emotions and with social injustice, for the epileptic is not just a nerve-muscle preparation; he is a person, in health an integrated combination of the physical, the mental, the social and the spiritual. Disruption of any part can cause or aggravate illness".

Lennox and Markham, 1953

Depression and epilepsy are both common conditions. Moreover, review of the literature suggests that depression is a frequent complication of epilepsy. Many common factors have been implicated in the pathogenesis of both disorders, such as psychosocial variables and biochemical abnormalities, including disorders of 5 Hydroxytryptamine (5HT), Noradrenaline (NA), Dopamine (DA), Gamma aminobutyric acid (GABA), Acetylcholine (ACh), sodium,folic acid (FA), and malfunctioning of the hypothalamic-pituitary axis. The question of laterality is controversial: do lesions lateralised to one hemisphere produce clinical pictures phenomenologically different from those in the opposite hemisphere? Suicide is common in both disorders, being roughly 30 times that of the general population in depression, 4 to 5 times that of the general population in all people with epilepsy, and 25 times that of the general population in the subgroup with temporal lobe epilepsy (TLE). However, little has been written about the relationship between depression and epilepsy and there have been no studies into the precise phenomenology of depression in the context of epilepsy.

Although the literature is controversial, the DST has been shown to be of some value in identifying a type of "melancholia", with certain clinical features and prognostic implications. There have been no studies of its usefulness in depressed epileptics.

There are many paradoxes in the treatment of the 2 disorders. Most antidepressants lower the seizure threshold and may provoke seizures clinically, while the majority of anticonvulsants lower mood. Carbamazepine (CBZ), a recognised anticonvulsant, is probably also psychotropic. Sodium valproate (VPA) is an anticonvulsant and may be antimanic. Electroconvulsive therapy (ECT) is antidepressant, as well as being an induced seizure. In addition, anticonvulsants and possibly antidepressants, induce hepatic enzyme systems. One can see that there would be difficulties in treating the conditions when they occur together, as the medication prescribed for one may have an effect on the other, and little is known about these interactions. Moreover, there have been no studies as to whether antidepressants alleviate the depression associated with epilepsy.

This thesis will consist of 2 parts. The first will be a parallel review of the literature exploring the possible links between depression and epilepsy. Previous investigations of depressed epileptics, and problems arising from having the 2 conditions will then be considered.

The second section involves 3 studies. The first investigates the phenomenology of the depression seen in people with epilepsy. The experiment was designed to answer the following questions:

1) Is the phenomenology of the depression seen in patients with epilepsy similar to that in patients without epilepsy: is it mainly endogenous or non-endogenous, and what is its severity? What is the degree of anxiety, neuroticism and hostility in the depressed epileptic? Does the depression occur in obsessoid or hysteroid individuals?

2) Do different groups of patients with epilepsy differ in the depressive syndrome with which they present; does the type of epilepsy, the site of a focal lesion, or the seizure frequency influence the phenomenology?

3) Is there a high incidence of depression, suicide, alcoholism or other psychiatric illness in the families of patients who present with depression and epilepsy; and, if so, is it associated with a particular type of depression?

4) What is the relationship between the depressive illness and the anticonvulsant drugs?

5) Is there any relationship between the red blood cell and serum FA and the severity or type of depression?

The second study investigates the usefulness of the DST in identifying certain clinical features, and indicating prognosis of the depressive illness in patients with epilepsy.

The third study deals with the treatment of depression in people with epilepsy, and involves a double blind antidepressant trial and a pharmacokinetic study. It was designed to answer the following questions:

1) Are antidepressant drugs clinically effective as antidepressants in depressed people with epilepsy?

2) Is any antidepressant effect related to serum antidepressant levels?

3) What effect does doubling the antidepressant dose have on antidepressant levels?

4) Do antidepressant drugs alter serum anticonvulsant levels?

5) Is there a relationship between serum antidepressant and anticonvulsant levels?

6) Do antidepressant drugs provoke clinical seizures in patients with epilepsy?

SECTION I

REVIEW OF THE LITERATURE

CHAPTER 1

DEPRESSION

1.1. History

Several historical reviews offer rich material on depression (Lewis 1934a; Whitwell 1936; Zilboorg 1941), and a brief summary will be compiled from them. The earliest mention of depression appears in the biblical story of King Saul (ca 1033 BC). Detailed clinical accounts of his life suggest an early "psychopathic tendency"; his prophecies occurred under "strong emotional tension". He then appears to have had a recurrent depression, some "ecstatic seizures", homicidal attempts and finally committed suicide by falling on his sword.

Melancholia had its recorded beginning in western medicine with Hippocrates (ca 460 - 357 BC). Melancholia was believed by Aretaeus (ca 100 AD) to be the beginning and even part of the disorder called "mania", an ancient foreshadowing of the manic-depressive concept. Galen, living in the second century suggested that melancholia depended on a superfluity of black bile "in the very substance of the brain"... which "causes melancholy symptoms to affect the mind". Lewis makes the point that from the time of Galen there is a "long blank in occidental psychiatry".

In the middle ages in the west, demonology became the speculative foundation of thought about mental illnesses. A fresh period began in the eighteenth century, in which the interaction of physical and mental factors was discussed, and many of the writers of the period noted that melancholia was one of the most important mental disorders. The therapy of melancholia in this period consisted of drugs of all sorts including arsenic, phosphorus, datura stramonium and belladonna, some of which had been used to treat epilepsy as well (Temkin 1971). William Cullen (ca 1829) described as "the creator and founder of the theory and practice of psychiatry in England" recognised both melancholia and mania, and believed that the latter occurred most frequently in persons with a melancholic temperament. Falret, in 1854, described "folie circulaire", a detailed and unmistakable description of alternating manic and melancholic mood swings, separated by periods of perfect lucidity, and drew attention to the difference between this, the periodic variety, and ordinary melancholia.

Kraeplin, between 1896 and 1920, was the father of the modern period of psychiatry, clearly distinguishing between mental diseases, especially dementia praecox, manic-depressive insanity and involutional melancholia. Since then, the literature has been vast, and the notion of depression, its precise nosology, classification, boundaries and aetiological theories have been controversial.

1.2. Definition and Description of Depression

Recent ideas about depression stem from the work of Kraeplin who formulated the concept of manic-depressive disease. This is defined as "a disorder in which a change of mood is the primary and central feature, mood being raised in the case of mania and lowered in depression" (Hamilton 1982). Hamilton describes the clinical symptoms of depression thoroughly, and makes the point that lowering of mood is not the central feature of minor forms of the illness, and may not occur at all in the controversial category of masked depression. Depressive symptoms are different from depressive illness (Snaith et al 1971). Depressive symptoms may constitute hopelessness, demoralisation, simple unhappiness or bereavement (Frank 1961; Wing et al 1978; Clayton et al 1972).

Depressive illness in this thesis will be defined according to the Research Diagnostic Criteria (RDC), (Spitzer et al 1978), characterised by the following: one or more distinct periods of dysphoric mood, with attendant sadness, depression, hopelessness or irritability, lasting at least 1 to 2 weeks, and for which help has been sought. In addition, at least 5 of the following 8 must be present: appetite changes, sleep disturbances, loss of energy, psychomotor agitation or retardation, loss of interest, feelings of reproach and guilt, impaired concentration and thoughts of death. No signs of schizophrenia must be present.

Depression is associated with a greater risk of suicide compared with the general population. In follow up studies of depressed or affective disorder patients over many years, the death rate for suicide is over 30 times greater than that of the general population without these disorders, and death by suicide approached 15% of deaths (Guze and Robins 1970).

Hamilton (1982) points out that when the illness is severe, the 3 symptoms of depressed mood, feelings of guilt and suicidal thoughts, generally regarded as central features of the illness, are present; the 3 most common symptoms, being found in almost every patient are depressed mood, loss of interest and anxiety. As early as 1934, Lewis (1934b) noted that anxiety

frequently occurred in his melancholic patients, and anxiety, as part of a depressive illness, is generally accepted by clinicians (Snaith et al 1971).

1.3. Classification of Depression

The classification of depression is a matter of controversy. Kendell (1976) reviewed the relevant literature and referred to the "contemporary confusion" which still exists. Table I summarises the various classifications of depression. Kendell (1976) traces the origins, pitfalls and positive features of current themes of classification. Debates as to an internationally accepted classification continue, but generally there are broad categories to which most people adhere and which will be used in this thesis.

The St. Louis group (Robins et al 1972) distinguished between primary and secondary depression. A primary affective disorder, for example depression, is one in which the first evidence of a diagnosable psychiatric illness is an affective episode; a secondary affective disorder is one in which the affective episode was preceded by another diagnosable psychiatric illness (Robins et al 1972). Leonhard (1959) and Perris (1966) described bipolar and unipolar illnesses. Bipolar illness represents bouts of both mania and depression; unipolar illness denotes recurrent mania or depression. Both these classifications are widely accepted.

Dunner (1980) suggests further classification of bipolar disease, mainly according to the severity of the mania, into 2 groups: bipolar I (patients whose severe mania has necessitated hospitalisation) and bipolar II (patients whose severity of mania did not result in such social disruption or hospitalisation). TCA*-induced hypomania is included as a bipolar II illness. It is further suggested that bipolar I and II illnesses have several different clinical characteristics.

The area where controversy still reigns is between endogenous (Type A, psychotic, melancholic, retarded) depression and non-endogenous (Type B, neurotic, reactive, exogenous, anxious-tense) depression. It has been pointed out that either type is incapable of definition and often means little more than "severe" and "mild" (Bowman and Rose 1951). The Newcastle School (Kiloh and Garside 1963; Carney, Roth and Garside 1965) suggest that patients' depression scores subjected to statistical analysis

*Tricyclic antidepressant

TABLE I: CONTEMPORARY CLASSIFICATIONS OF DEPRESSION (From Kendell 1976)

A. Simple Typologies

One Category

Lewis

Depressive illness

Two Categories

Roth

Endogenous depression

Neurotic depression

Pollitt (1965)

Physiological S Type depression

Physiological J Type depression

Van Praag (1965)

Vital depression

Personal depression

Three Categories

ICD-6

Manic-depressive reaction
Involutional melancholia
Neurotic depressive reaction

Overall (1966)

Anxious-tense depression
Hostile depression
Retarded depression

Four Categories

ICD-8

Manic-depressive psychosis, depressed type
Involutional melancholia
Reactive depressive psychosis
Depressive neurosis

Paykel (1971)

Psychotic depression
Anxious depression
Hostile depression
Young depressives with personality disorder

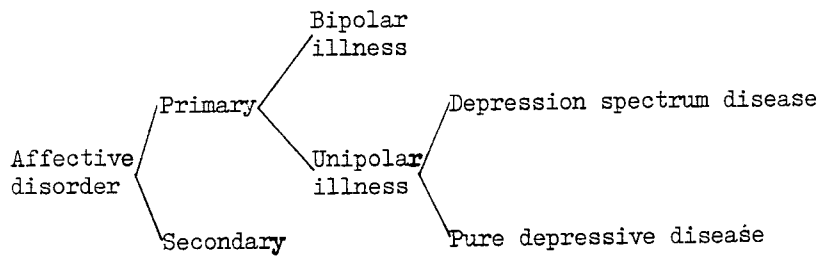
Five Categories

Blinder (1966)

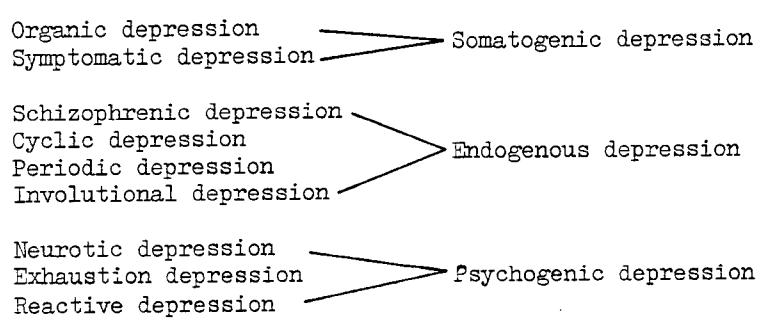
Physiological retardation depression
Tension depression
Schizo-affective depression
Depression secondary to a problem in living
Depression as the prodrome of organic illness

B. Tiered Typologies

Winokur



Keilholz (1972)



C. Dimensional Systems

Kendell (1968) One dimension (Psychotic/Neurotic)

Eysenck (1970) Two dimensions (Psychoticism and Neuroticism)

are bimodally distributed, and that there is a clear cut boundary between endogenous and reactive depressions. Others (Kendell and Gourlay 1970) view the distribution of depression scores of their patients as unimodal and thus see a psychotic/neurotic continuum. In a later paper from the Newcastle School, (Carney and Sheffield 1972) it was felt that a compromise could be reached - that neurotic depression is dimensional, and endogenous depression categorical. This means that the 2 are not mutually exclusive, and that an individual could have endogenous depression with neurotic features as well. Mendels and Cochrane (1968) suggested that Type A was a pure depressive illness, while Type B depression was mixed, and diluted with other syndromes - "the so-called endogenous factor might represent the core of depressive symptomatology, whereas the clinical features of the reactive factor may represent phenomenological manifestations of psychiatric disorders other than depression which contaminate the depressive syndrome". Kiloh et al (1972) suggested that Type A or endogenous depression was a disease entity with a biological basis, but Type B simply one facet of the broad spectrum of neurotic reactions to stress.

In conclusion, most people accept endogenous depression as a syndrome with certain characteristic clinical features, genetic predisposition and biological abnormalities. At the other end of the distribution are the non-endogenous illnesses, a heterogeneous group of syndromes, most of which have in common the change of mood characteristic of depression.

1.4. Epidemiology of Depression

Two comprehensive reviews (Boyd and Weissman 1982; Hirschfield and Cross 1982) have appeared recently, as has a clear description of the course of affective illnesses (Angst 1981), and a summary of their conclusions will be presented. The point prevalence (that proportion of the population which has a disorder at a given point in time) of non-bipolar depression in industrialised nations is 3.2% of the adult male population, and 4.5% to 9.3% of the adult female population. The incidence (number of new cases in the population per year) of non-bipolar depression is 82 to 201 per 100,000 men per year, and 247 to 7800 per 100,000 women per year. Risk factors for non-bipolar depression are: being female, particularly in the age group 35 to 45 years; having a family history of depression or alcoholism; having childhood experiences in a disruptive, hostile and generally negative environment in the home; having had recent negative

life events; lacking an intimate confiding relationship; having had a baby in the preceding 6 months. Non-bipolar depressive disorder has a later mean average age of onset (45 years) than does bipolar depressive disorder (35 years).

No community-based studies of urban-rural differences in rates of depression are known, although, in general, studies comparing rates of mental illness in rural versus urban settings report higher overall rates in urban populations. No differences in rates of non-bipolar depression have been reported among members of different religious groups, nor among blacks and whites. Survey studies report a slightly higher prevalence of non-bipolar depression among persons of lower socio-economic classes.

The incidence of bipolar disorder for men is 9 to 15.2 new cases per 100,000 per year, and for women 7.4 to 32 new cases per 100,000 per year. Risk factors for bipolar disorder are being female and having a family history of bipolar disorder. Bipolar disorder seems to be associated with the upper socio-economic class. Bipolar depression has been found to be more prevalent in members of certain religions such as the Hutterites from the midwest in the United States of America (USA), and Ashkenazi Jews.

There is a tendency for affective disorder to recur. This is especially true for bipolar disorders and schizo-affective psychoses, whereas unipolar depressions have a more favourable course.

1.5. Aetiology of Affective Disorders

1.5.i. Genetics

Genetic aspects of the predisposition to affective illness have been investigated in recent years by a number of workers. The famous early twin study work was that of Kallmann (1950) who found concordance rates in the twins were 96% in monozygotic and 26% in dizygotic twins. Stenstedt (1952) suggested that the factor responsible was a single autosomal dominant gene of reduced penetrance and somewhat variable expressivity. In his work on manic-depressive psychosis, he found that approximately 12% of the first degree relatives of his probands suffered from a manic-depressive psychosis, and that there was no excess of psychiatric disorder of other kinds. Similar findings were made by Kay (1959) and Hopkinson (1964). The latter 2 authors, however, indicated that the total group of affective illnesses may have different aetiologies characterised by the different ages of onset of the

psychosis; the forms with early onset, associated with a significant family history for affective disorder, were those genetically determined.

Alternative hypotheses have not been lacking. On the basis of a review of the literature, Ordonez Sierra, cited in Meyer-Gross et al (1974) proposed a two-gene theory: gene A the phasic gene, and gene B inhibiting its manifestation, both dominant, but with different frequencies. Leonhard et al (1962) offered a similar model. He and co-workers undertook an investigation using 104 female patients with affective psychoses, and they found they could be classified into 42 women with bipolar illness and 62 women with monopolar (unipolar) illness. The parents, the sibs, and the sibs of the parents of the bipolar patients all showed higher incidences of affective psychoses than the corresponding relatives of patients with unipolar depressive syndromes. The authors concluded that manic-depressive illness (manich-depressive krankeit), true melancholia (reine melancholie) and true depression (reine depressionen) are to be regarded as genetically distinct.

Perris (1966) presented clinical and genetic evidence to suggest that manic-depressive psychosis is a heterogeneous disorder consisting of 2 distinct types: unipolar, characterised by recurrent episodes of depression only, and bipolar, in which both mania and depressive episodes occur. Evidence for a genetic contribution to the aetiology of manic-depressive psychosis comes from both twin and family studies and has been summarised by Slater and Cowie (1971). Table 2 shows the concordance rates in twins of manic-depressive patients, adapted from Slater and Cowie (1971) and Allen et al (1974).

There have also been more recent twin studies (Bertelsen et al 1977) and adoption studies (Mendlewicz and Rainer 1977) which have consistently shown a familial pattern of distribution of bipolar affective disorder. Others (Winokur and Clayton 1967; Singh et al 1979) also provided data supporting the division of manic-depressive psychosis into the unipolar and bipolar groups - each with its distinct genetic mechanism and clinical manifestations. Most studies indicate that first degree relatives of patients with depression have an increased incidence of the disorder, relatives of bipolar probands tending to have bipolar disorders and those of unipolar probands, unipolar disorders (Perris 1966; Brodie and Leff 1971). Perris (1966) also concluded that the overall heredity for psychoses is greater in bipolar than unipolar probands. At least 2 recent studies, however, (Tsuang 1978; Taylor et al 1980) found a high proportion

TABLE 2: CONCORDANCE RATES IN TWINS OF MANIC-DEPRESSIVE PATIENTS

Author	Year	Country	Type of Illness	Monozygotic Twins		Dizygotic Twins	
				No. of Pairs	% Concordance	No. of Pairs	% Concordance
Luxenburger	1928	Germany	Bipolar	4	75	13	0
Rosanoff et al	1935	USA	Bipolar	23	70	67	16
Kallmann	1950	USA	Bipolar	23	96	52	26
Slater	1953	England	Bipolar	3	67	13	23
			Unipolar	5	40	17	24
da Fonseca	1959	England	Both	21	75	39	39
Harvald and Hauge	1963	Denmark	Bipolar	15	67	40	5
Kringlen	1967	Norway	Bipolar	6	33	9	0
Pollin et al	1969	USA	Both	24	4	58	0
Allen et al	1974	USA	Bipolar	5	20	15	0
			Unipolar	10	40	19	0

of unipolar illness in the relatives of bipolar probands and bipolar illness in the relatives of unipolar probands. Winokur (1972) suggested that there are 2 types of depressive illness, depression spectrum disease and pure depressive disease with different genetic mechanisms.

Many workers have found a female preponderance in affective disorders (Slater and Cowie 1971), especially female sibs of probands (Winokur and Clayton 1967) and among affected offspring of bipolar probands (Reich et al 1969; Mendlewicz and Rainer 1974; Waters and Marchenko-Bouer 1980). Others report a female preponderance in unipolar illness (Perris 1966; Winokur and Clayton 1967; Bertelsen et al 1977; Angst and Zerbin-Rüdin, cited by Bertelsen et al 1977). On any hypothesis, the relatively greater incidence of affective psychoses in the female than in the male requires explanation. Rosanoff et al (1935) first suggested that an X-linked dominant gene is involved and this was later suggested by a statistical experts (Burch 1964), who also noted that statistical features of the disorder closely resembled comparable features of diseases that were

widely believed to have an auto-immune aetiology. Several studies have suggested the possibility of a single dominant gene located on the X-chromosome in the bipolar group (Reich et al 1969; Winokur and Tanna 1969; Mendlewicz et al 1972a; Mendlewicz and Rainer 1974). Other researchers (Green et al 1973; Goetzl et al 1974; Gershon et al 1975; Smeraldi et al 1977) are not in agreement with this. Other studies support an X-linked transmission, but only in the unipolar group (Perris 1966; Singh and Agrawal 1980).

At least 2 studies have implicated a connection between blood group O and bipolar illness (Shapiro et al 1977; Singh et al 1979). A number of studies (Perris 1971; Slater et al 1971; Smeraldi et al 1977; Singh and Agrawal 1980) have reported data consistent with a polygenic pattern of inheritance for affective illness.

Other investigators have noted higher prevalence of alcoholism among relatives of ill probands (Winokur and Clayton 1967; Mendlewicz et al 1972b), especially in those with bipolar illness (Taylor and Abrams 1973), male relatives being mostly affected (Goetzl et al 1964; Pitts and Winokur 1966), or unipolar illness (Singh and Agrawal 1980).

A high incidence of suicide in the relatives of bipolar patients has been demonstrated by others (Stenstedt 1952; Pitts and Winokur 1964; Brodie and Leff 1971; Mendlewicz et al 1972b). Some authors report an increased risk of suicide using twin studies (Juel-Nielsen and Videbach 1970; Bertelsen et al 1977), though this was refuted by Kallmann et al (1949), which was not as comprehensive a study as the 2 former.

In the recent past other criteria for investigation have been employed: presence or absence of family history (Mendlewicz et al 1972b), early or late onset of illness (Taylor and Abrams 1973), morbidity risk (Mendlewicz and Rainer 1974) and response to drugs (Pardue 1975). The difference between patients who respond to mono-amine-oxidase inhibitors (MAOIs) and those who respond to the imipramine group of antidepressants may, indeed, be based on genetic factors (Angst 1961; Pare et al 1962; Pare and Mack 1971) as first degree relatives who become depressed, will also respond to these drugs in a similar way.

In conclusion, it can be said that to date no absolute consensus of opinion has evolved. However, genetic vulnerability seems to have been fairly clearly demonstrated in bipolar illness and recurrent unipolar depressions.

1.5.ii. Psychosocial Theories of Depression

Various models of depression, reflecting the dominant schools of thought are summarised in Table 3. Abraham (1911) and Freud (1917) lead the psychoanalytic field, and viewed depression as representing the repression of sadism and the introjection of the aggressive instinct or hostility, triggered by the loss of an ambivalently loved object, and not directed at the appropriate object. The model, formulated in the days of ID psychology and which is essentially phrased in metapsychological terms, is the most widely quoted psychological explanation of depression, yet is difficult to verify. Epidemiological data have demonstrated an inverse relationship between suicide and homicide (Kendell 1970). These broadly reflect introverted and extraverted hostility and are therefore grossly compatible with this model. In several clinical studies which will be reviewed in the section on the "Hostility and Direction of Hostility Questionnaire", patients recovering from a depressive illness show reductions in the amount of hostility and intropunitiveness. Some investigators (Overall et al 1966) identified a group of "hostile depressives" characterised by the concomitant presence of depression and outwardly expressed anger. Many have felt that early childhood experiences determine types of psychopathology in later life. Klein (1935; 1940) saw as the precipitant of depression, the experience of loss in the first year of life at the time of weaning. The way in which the infant responded at that time was seen by her as a determinant of the way the adult would respond to future losses. Spitz (1946) coined the term "anaclitic depression", while Robertson and Bowlby (1952) and Bowlby (1980) described phases of "protest", "despair" and "denial", which resulted from separation from their mothers around 6 to 8 and 18 to 24 months respectively. Bibring (1965) sees lowered self-esteem as central in the development of depression, which can be defined as "the emotional correlate of a partial or complete collapse of the self-esteem of the ego, since it feels unable to live up to its aspirations ..... while they are strongly maintained".

The main proponent of the cognitive model of depression is Beck (1967; 1971). According to this viewpoint, hopelessness and helplessness represent the central features of depression and reflect a "negative cognitive triad" of conception of the self, interpretations of one's experiences and view of the future. This model emphasises the role that disturbances in thinking play in determining emotional states. Depressed patients tend to interpret their experiences in terms of their being deficient or deprived: helplessness and hopelessness about "undoing" the loss or deficit seem to be essential features of depression.

TABLE 3: PSYCHOSOCIAL MODELS OF DEPRESSION

(Modified from Akiskal and McKinney 1975)

School	Date	Proponent	Model	Mechanism
Psycho Analytical	1911	Abraham	Aggression turned inward	Conversion of aggressive instinct into depressive affect
	1917	Freud		
	1935	Klein	Object relations	Failure to internalise a good object
	1946	Spitz	Object loss	Separation: disruption of an attachment bond
	1952	Robertson and Bowlby	"	
	1980	Bowlby	"	
	1965	Bibring	Loss of self-esteem	Helplessness in attaining goals of ego-ideal
Psychological And Behavioural	1955	Kelly	Personal construct theory	Constriction
	1967	Beck	Negative cognitive set	Hopelessness
	1972	Seligman	Learned helplessness	Uncontrollable aversive stimulation
	1968	Lazarus	Loss of reinforcement	Rewards of "sick role" substitute for lost sources of reinforcement
	1973	Ferster		
	1975	Lewinsohn		
	1969	Burgess	Reduced reinforcement	Subject's response frequency or quality diminishes because of reduced reinforcement
	1977	Rehm	Self control	Deficits in self control result in insufficient self reward and excessive self punishment
Sociological	1969	Paykel et al	Life events	Exit and undesirable events precede depression
	1973	Brown et al		Precipitating events "bring forward" occurrence of depression
	1978	Brown and Harris		Vulnerability factors
	1974	Bart	Sociological	Loss of role status
Existential	1964	Becker	Existential	Loss of meaning of existence

Kelly (1955; 1963), using the Personal Construct Theory, views man as an intuitive scientist seeking to predict future events. This theory views depression as the result of an individual who, throughout life, has found circumstances confusing as a result of an inappropriate construct system and has consequently limited his range of activities.

There are several behavioural formulations of depression. Seligman and his co-workers (Seligman 1972) introduced the concept of "learned helplessness" to describe the interference with adaptive responding produced by inescapable shock, initially described in experiments with dogs, but later applying to humans as well. They hypothesised that it is not the shock or trauma per se, but only uncontrollable shock or trauma that produces failure to escape. "Depression" applies to passive individuals who believe they cannot do anything to relieve their suffering. There have been recent criticisms of the model (Costello 1978; Rizley 1978), but Seligman and colleagues (Abramson et al 1978; Seligman 1978) reformulated the theory and, in addition, proposed that the theory may pertain to a subclass of depression. Other proponents of behavioural theories of depression include Lazarus (1968), Ferster (1973), Lewinsohn (1975), Burgess (1969) and Rehm (1977).

Bart (1974) views depression in sociological terms and points out how loss of role status can predispose an individual to depression.

In recent years it has become apparent that life events occur with greater than chance frequency before the onset (Paykel et al 1969) or relapse of depressive episodes (Paykel and Tanner 1976), and the events particularly implicated are "exit" events or undesirable, stressful events. Brown et al (1973) also found that life events occurred prior to a depressive illness, and derived an index, "brought forward time", which corresponds to the average time by which spontaneous onset may be considered to have been advanced by the life events. Brown and Harris (1978) wrote extensively on the social origins of depression. They described women in a London borough: while almost all the women who developed depression in the time of the survey had experienced a severe life event, only a fifth of those with such provoking agents became ill. They proposed 5 "vulnerability factors" which contributed to depression only in the presence of a provoking agent. The 5 vulnerability factors suggested were as follows: 1) working class environment; 2) lacking a confidant; 3) loss of a mother before the age of 11 years; 4) 3 or more children under the age of 14 living at home; 5) lack of employment outside the home. In addition to the vulnerability factors, they described

precipitating events: in almost half of the sample of females suffering from depression, the precipitating life event consisted of a serious loss or disappointment.

Becker (1964) puts forward the existentialist view, that depression supervenes when the individual discovers that his world has lost its meaning and purpose.

1.5.iii. The Biological Theories of Depression

The biological basis of depression is complex and controversial, several theories having been advanced. The first was the catecholamine hypothesis, implicating deficient NA or DA. The second involved decreased indoleamines, especially 5HT. The third or "permissive" amine hypothesis attempted to reconcile the 2 previous hypotheses, suggesting that a 5HT deficiency renders an individual susceptible to an affective disorder; if catecholamine levels then decrease, depression occurs. Other neurotransmitters such as Ach and GABA have been implicated as abnormal in affective illness. More recently, attention has focussed on cyclic AMP and receptor abnormalities. Various electrolyte, biochemical and endocrine abnormalities have been noted, but it is difficult to confirm whether these are cause or effect. Each area will be considered in detail, especially the neurotransmitters and substances which have been implicated in, or reported as abnormal, in patients with epilepsy.

The monoamine and neurotransmitter hypotheses

Alterations in man's affective state induced by environmental events are a normal and familiar occurrence. The biochemical changes are therefore unlikely to be qualititatively different (Ridges 1975); instead they are likely to be quantitative changes, perhaps highly localised within the brain, reflecting merely exaggerated intensity or duration of a depressive reaction which is typical of the clinical condition (Spencer 1977). Brain amines have many roles in relation to mammalian behaviour (Baldessarini 1972). In turn, the vast majority of psychotropic drugs can be shown to affect in the brain, one or more of the following transmitters: NA, DA, 5HT and ACh (Spencer 1977).

The impulse to study brain amines in relation to depressive illness was provided by pharmacological observations made in the 1950's with the widespread use of reserpine in psychiatry and hypertension. Reserpine (rauwolfia) induced depression in 7% to 26% of patients (Muller et al 1955; Harris 1957; Faucett 1958) and it was possible that this effect of reserpine was due to a substantial depletion of brain amines. Rosenblatt et al (1960) were amongst the first to suggest that changes in catecholamine or indoleamine function might be involved in the appearance, as well as the abolition, of depression. A functional deficit of brain DA or NA was clearly behind the attempt by Pare and Sandler (1959) to treat depression with the catecholamine precursor dihydroxyphenylalanine (DOPA), and, later, the puzzle was possibly completed by the demonstration that the reserpine-induced effects including a depressive syndrome, in laboratory animals, could be abolished by treatment with the antidepressant imipramine (Sulser et al 1962) and the MAOIs (Spencer 1967).

The picture according to some, however, seemed to be more one of non-specific sedation rather than depression, demonstrated by the animal studies carried out by McKinney et al (1971). In addition, although some clinical surveys reported a 20% incidence of depression in patients treated with reserpine, criticism of the diagnostic criteria used in such surveys culminated in a careful review (Goodwin et al 1972) from which it was concluded that these agents precipitated depression only in predisposed individuals, for example, those with a past history of the disorder. In one prospective study (Bernstein and Kaufman 1960) of 50 patients who were treated with reserpine for a year, no cases of true depression were encountered, but 12 of the patients showed physical retardation and complained of tiredness: there was no subjective depressive mood in these patients who, the authors suggested, were suffering from "pseudo-depression".

Substantial increases in our knowledge of the biochemical pathways of transmitter amines were made in the early 1960's and a summary of the position today is given in Figures 1 and 2.

The catecholamine hypothesis

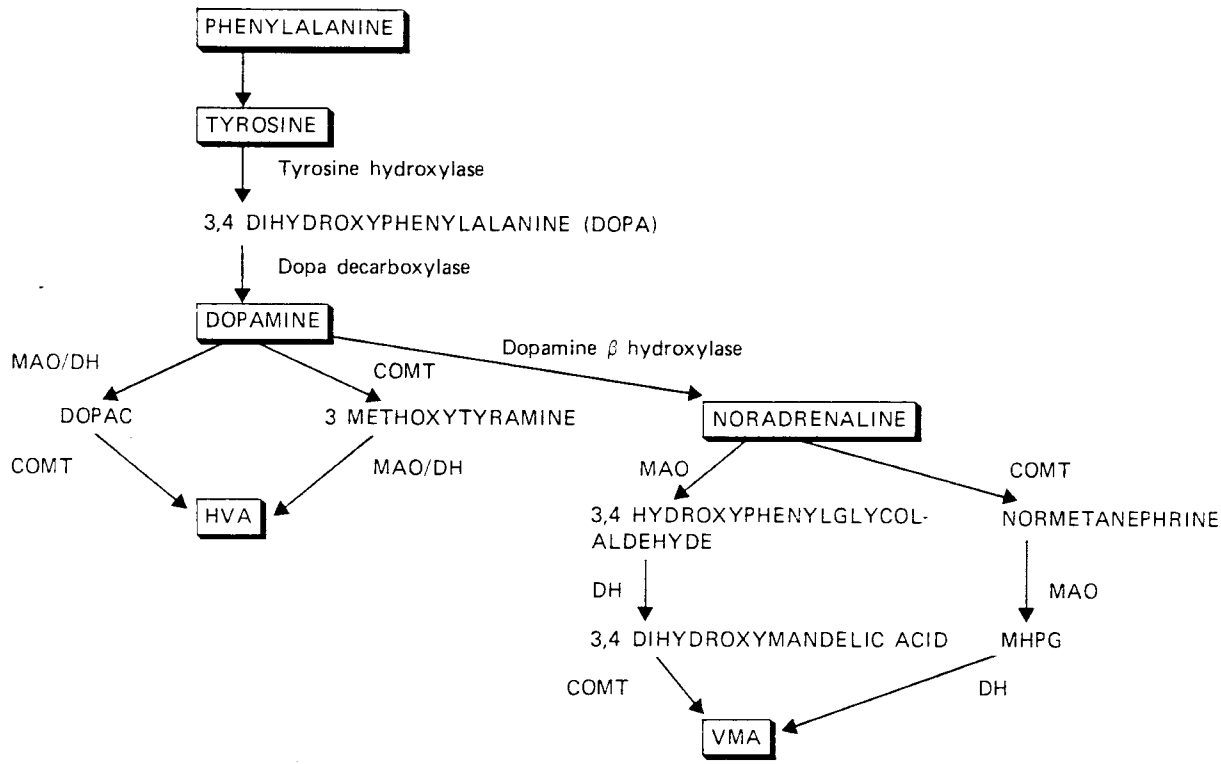
Schildkraut's (1965) classic catecholamine hypothesis of affective disorders proposed that "some, if not all, depressions are associated with an absolute or relative deficiency of catecholamines, particularly NA at functionally important adrenergic receptor sites in the brain.

Elation conversely may be associated with an excess of such amines". At about the same time, Bunney and Davis (1965) also suggested a catecholamine deficit in depressive illness.

Disorders of monoamine metabolism in man can be studied in 3 ways: the measurement of metabolites and parent compounds in body fluids, mode of action of drugs and post-mortem studies.

The major catecholamine hypothesis holds that in depression there is a deficit of NA metabolism (Schildkraut 1965). This hypothesis is based on observations that cerebrospinal fluid (CSF) levels of the NA metabolite MHPG is lower in depressed patients (Gordon and Oliver 1971; Post et al 1973a; Jimerson et al 1975). These studies are somewhat complicated by the fact that MHPG occurs both free and as the sulphate ester, and in these studies only total changes were assessed (Green and Costain 1979). In addition, Åsberg et al (1978) found normal CSF levels of MHPG in depressed patients. The acid metabolite of NA, VMA, has also been reported to be low in the CSF of depressed patients (Jimerson et al 1975). Christensen et al (1980) found mean adrenalin concentration in CSF to be lower in depressed patients compared with controls, while CSF NA showed no differences between the 2 groups. Since renal MHPG is regarded as a gross indicator of extraneuronal NA degredation in the Central Nervous System (CNS) (Karoum et al 1975), many studies have investigated urinary MHPG and found it to be low in depressed patients (Maas et al 1968; Bond et al 1972; Deleon-Jones et al 1975). Schildkraut (1975) makes the point that low urinary MHPG may be characteristic of a particular subgroup of depressive disorders. It may apply, in particular, to patients with bipolar depression (Greenspan et al 1970; Deleon-Jones et al 1975). The phenomenon was observed in patients with motor retardation as well as in agitated patients (Deleon-Jones et al 1975), suggesting that the low MHPG excretion is therefore unlikely to be a phenomenon of peripheral origin, determined by patients' state of activity. Goode et al (1973) also presented data suggesting that urinary MHPG levels are independent of exercise and psychomotor activity. Bunney et al (1967) found increased levels of VMA and NA in the urine of psychotic but not neurotic depressives.

Shaw et al (1973) found CSF MHPG in unipolar depressed patients to be similar to that of a control group. After recovery there was a small but significant decrease in the MHPG concentration; there was also a positive correlation between the MHPG concentration and the severity of depression. On recovery there was a significant rise in urinary MHPG which is consistent with other reports (Maas et al 1968). There was, however, no correlation between urinary and CSF MHPG.



MAO	Mono amine oxidase
DH	Dehydrogenase
COMT	Catechol - o - methyltransferase
VMA	3-methyoxy - 4 - hydroxy-mandelic acid
HVA	Homovanillic acid
MHPG	3-methoxy - 4 - hydroxyphenylglycol

Figure 1

MAIN CATECHOLAMINE METABOLIC PATHWAYS *(from Green & Costain 1979)*

Maas (1975) defines the NA deficient patients as "Group A" depressives. They are those who have low MHPG in urine; no change in urinary MHPG following treatment with imipramine or desipramine; mood responds to administration of imipramine or desipramine (Bunney et al 1967; Fawcett et al 1972; Maas et al 1972; Beckmann and Goodwin 1975); an elevation of mood with dexamphetamine (Fawcett et al 1972) and failure to respond to amitriptyline. This is somewhat confusing, as most authors agree that imipramine and desipramine have differential actions on the monoamines: desipramine has a much more marked inhibitory effect on re-uptake of NA into the neurone than on re-uptake of 5HT, while imipramine has a slight but significant effect on NA re-uptake, as well as affecting 5HT (Carlsson et al 1969a; 1969b; Ross and Renyi 1969). Maas et al (1972) reported that in those patients who responded to imipramine or desipramine and having the low baseline urinary MHPG level, the MHPG level slightly increased or did not change after 4 weeks of treatment. In contrast, the patients who had a normal or high baseline MHPG concentration (which will be discussed later as a group) had poor responses to imipramine and desipramine, with baseline levels decreasing by the fourth week of treatment.

Goodwin and Potter (1979) reviewed 15 studies investigating urinary MHPG in depression. In spite of inter-study variation in absolute values, the overall mean urinary MHPG for all depressed patients was 25% lower than of normal controls. In addition, the subgroup of bipolar depressed patients consistently had lower urinary MHPG than controls: in contrast, the unipolar depressives in different studies had varying MHPG values. They also put forward the suggestion that depressions which involve considerable anxiety will not be associated with low MHPG.

Cautionary notes to the NA deficit hypothesis are that investigators have reported normal CSF MHPG values in depressed patients (Wilk et al 1972; Shopsin et al 1973), especially those with unipolar illness (Shaw et al 1973). There is, moreover, some controversy as to the significance of MHPG levels. Although some authors (Goode et al 1973; Deleon-Jones et al 1975) suggested urinary MHPG levels were independent of motor activity, the work of others suggested the opposite (Post et al 1973b). Post et al (1973c), moreover, suggested that the spinal cord contributes to the concentration of CSF MHPG. Wyatt et al (1971) found that the total resting plasma adrenalin and NA were increased in depressed patients when compared to controls. Post-mortem findings have also failed to support the hypothesis: no change in brain NA was found in brains of suicidal patients (Bourne et al 1968; Pare et al 1969; Moses and Robins 1975).

In conclusion, the bulk of evidence points to the involvement of central NA systems in the pathophysiology of at least some forms of major affective illness, especially those with bipolar features.

A variant of the catecholamine hypothesis is the Dopamine Hypothesis which is based on observations that some depressed patients have low HVA in their CSF (Roos and Sjöström 1969; Nordin et al 1971; Papeschi and McClure 1971; Mendels et al 1972; Åsberg et al 1978; Kasa et al 1982), especially if the method of probenecid accumulation is used (Goodwin et al 1973). Goodwin et al (1973) also noted that within the group of depressed patients, HVA accumulation was higher in bipolar than in unipolar depressives. Several authors (Curzon et al 1971; Post et al 1973c; Young et al 1973; Garelis et al 1974) have shown that lumbar CSF HVA is derived from the brain, the last authors indicating that the largest contribution is probably made by the nigrostriatal DA system. In addition, some patients respond clinically to DA agonists such as nomifensine (Hunt et al 1974; Costall et al 1975; Braestrup and Scheelkrüger 1976). According to Goodwin et al (1973), the disorder of DA metabolism is most marked in endogenous depressives with a unipolar course.

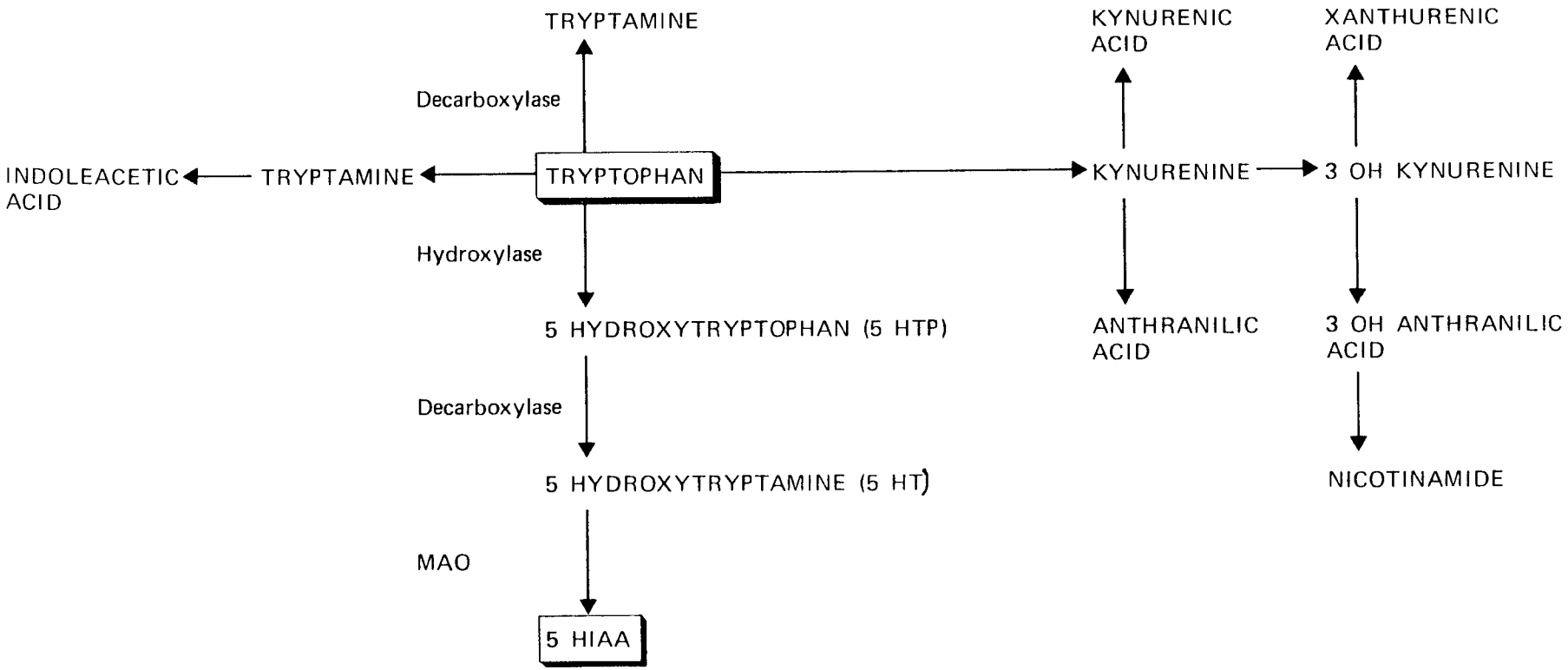
There is, however, evidence against the hypothesis. The school of van Praag found that decreased HVA was a phenomenon related to the state of motor retardation and not a characteristic of endogenous (vital) depression (van Praag and Korf 1971; van Praag et al 1973; van Praag et al 1975). Normal CSF HVA values have been reported by others in depressives (Bowers et al 1969). Post-mortem studies have failed to reveal any abnormalities in DA metabolism (Pare et al 1969; Moses and Robins 1975).

Sachar et al (1973) reported that in response to both insulin-induced hypoglycaemia and L Dopa, unipolar depressed patients secreted less growth hormone (GH) than did normal controls and bipolar subjects. Prolactin (PRL) responses to L Dopa were normal for nearly all subjects. Since it is believed that PRL responses are mediated by brain DA, and GH responses by brain NA, these data tend to support the hypothesis that there is a disturbance of brain NA metabolism in unipolar depressives.

The 5 Hydroxytryptamine (5HT: serotonin) hypothesis

The fact that reserpine also depleted brain 5HT led to an hypothesis implicating a functional deficit of brain indoleamines in depression (Coppen 1972). The principal degradation product of the central 5HT metabolism is 5HIAA (See Figure 2). There have been many studies investigating CSF 5HIAA. Low levels of 5HIAA in the CSF of depressed patients were first reported by Ashcroft and Sharman (1960). Since then, decreased values of CSF 5HIAA have frequently been reported in patients with depression (Ashcroft et al 1966; Dencker et al 1966; Bowers et al 1969; Papeschi and McClure 1971; Coppen et al 1972a; McLeod and McLeod 1972; Mendels et al 1972; Ashcroft et al 1973; Coppen 1973; Bridges et al 1976), especially if the method of probenecid accumulation is used (van Praag et al 1970; van Praag et al 1973). Most, but not all, of the studies reached significant values. The probenecid technique is based on the fact that the concentration of 5HIAA in CSF depends not only on the synthesis rate of 5HIAA, but also on the active transport mechanism which removes it from the CSF, and which is blocked by probenecid, thus magnifying differences between patients and controls (Åsberg and Bertilsson 1979). Bridges et al (1976) found decreased 5HIAA values in the ventricular CSF of depressives. Coppen's (1973) data showed a mean 5HIAA value in depressives approximately half that of controls; of particular interest was the observation that values did not return to normal on recovery, which confirmed previous findings (Bowers et al 1969; Coppen et al 1972a). Others have indicated that the decrement in CSF 5HIAA did not correlate with the severity of the depression (Coppen et al 1972a; McLeod and McLeod 1972). Some authors, on the other hand, demonstrated a rise to normal 5HIAA values on recovery after treatment (Dencker et al 1966; Garattini et al 1967).

Åsberg et al (1973) pointed out that CSF 5HIAA has a positive correlation with age, and there is a tendency for females to have higher values than males. In a later study (Åsberg et al 1978) showed that depressed patients had a significantly lower CSF 5HIAA than age and sex matched controls, and similar results when patients were matched for age and height rather than sex (Åsberg and Träskman 1981), as previously it was shown that the sex difference in 5HIAA in the CSF could be partly accounted for by an inverse correlation between body height and the metabolite concentrations (Åsberg and Bertilsson 1979). Later studies by the same group (Åsberg et al 1973; 1976a;1976b) demonstrated that within a group of patients with endogenous depression, the CSF 5HIAA concentrations showed a bimodal distribution.



OH Hydroxy
5 HIAA 5 Hydroxyindoleacetic acid
MAO Mono amine oxidase

Figure 2

MAJOR INDOLEAMINE METABOLIC PATHWAYS.

Compiled from : Curzon & Bridges 1970
Frazer et al 1973
Green & Costain 1979

This suggests that the group of endogenous depressions, despite tending towards homogeneity in terms of symptomatology, may be a heterogenous group in biochemical terms, and that a subgroup has a disturbance of 5HT function.

In addition, Åsberg et al (1976b) found that patients in the low 5HIAA mode attempted suicide significantly more often than those in the high mode, and they, moreover, used more violent means: in addition, patients in the lower mode were more successful in their attempts. Brown et al (1979) initially found that aggression and suicide were associated with lower levels of CSF 5HIAA in patients with personality disorders without affective illness. Later, Brown et al (1982) found aggression and suicide in patients with personality disorders without major affective disorder, were associated with each other, and with lower levels of CSF 5HIAA. The results of the Asberg group and those of Brown and colleagues may indicate that altered 5HT metabolism is associated with aggression and suicide, whatever the clinical diagnosis.

The finding of low CSF 5HIAA in depressed patients is somewhat complicated by the fact that the lower levels might be partially accounted for by concomitant drug treatment, since tricyclic antidepressant drugs (TCAs) have been shown to reduce the concentration of CSF 5HIAA (Papeschi and McLure 1971; Bowers 1972; Åsberg et al 1973; Mendlewicz et al 1982a). It has been suggested that this decrease is probably due to a feedback mediated reduction of transmitter synthesis (Åsberg and Träskman 1981).

There have, however, been a few reports of normal values of CSF 5HIAA in depression (Roos and Sjöström 1969; Nordin et al 1971; Wilk et al 1972). Post et al (1973b) evaluated the effect of psychomotor activity on CSF 5HIAA, and concluded that they were correlated, lowest results being in depression. There has also been disagreement as to the significance of CSF 5HIAA levels. Some studies on subjects with a block in CSF flow have found little decrease in CSF 5HIAA levels, suggesting a possible spinal origin for the 5HIAA (Curzon et al 1971; Young et al 1973). Several other authors, however, have argued convincingly that CSF 5HIAA reflects central metabolic changes of 5HT (Ashcroft et al 1973; Weir et al 1973; Garelis et al 1974).

Sedvall et al (1980) reported that, among normal subjects, those with a CSF 5HIAA below the median have a 2.7 times higher probability of having a family history of affective illness than those with values above the median.

Other evidence for a 5HT deficiency in depression, is the data that in depressed patients there may be abnormal tryptophan metabolism in the brain (Lapin and Oxenkrug 1969; Coppen 1972). Various studies have found low free tryptophan in the plasma of depressed patients (Aylward 1973; Coppen et al 1973; Kishimoto and Hama 1976; Coppen and Wood 1978). In the last study, the levels increased significantly after recovery, although they did not return to normal, as did those of Kishimoto and Hama (1976). In contrast, other authors (Niskanen et al 1976; Peet et al 1976; Riley and Shaw 1976) were unable to find such changes in plasma tryptophan in depression, although the last group (Riley and Shaw 1976) found that the group of unipolar patients who did not respond to TCAs had significantly lowered total plasma tryptophan. Coppen et al (1972b) reported lowered CSF tryptophan in depressives, but this was not confirmed by Ashcroft et al (1973).

Changes in the rate of peripheral tryptophan metabolism might be reflected in increased excretion of tryptophan metabolites. In depressed patients there have been reports of increased excretion of kynurenine, 3-hydroxy-kynurenine and xanthurenic acid (Cazzullo et al 1966; Rubin 1967; Curzon and Bridges 1970), although this has been disputed by Frazer et al (1973); this study, however, involved small numbers of patients.

Urinary 5HIAA or 5HT estimations have virtually no value in assessing brain 5HT function since about 90% of the amine and metabolite are derived from extracerebral sources (Boullin 1978).

The fact that blood platelets store and metabolise 5HT in a manner rather similar to that seen at nerve endings, has led to suggestions that platelets might be used as a neuronal model (Paasonen 1965; Stahl 1977; Boullin 1978). Some attention has been focussed on platelet 5HT mechanisms during depression, but few changes found suggested there was no change in 5HT uptake by platelets of depressed patients (Shaw et al 1971). Several authors, however, have found that the 5HT uptake by platelets of depressives was much less than that of controls (Tuomisto and Tukiainen 1976; Scott et al 1979; Coppen and Wood 1980): moreover, it is still reduced after clinical improvement (Coppen and Wood 1980). Since this transport is an active process, coupled to ATPase, activity of the enzyme has been studied in

depressed patients, but with conflicting results (Hesketh et al 1977; Scott and Reading 1978).

Post-mortem studies have provided data suggestive of decreased 5-hydroxyindole concentrations in the brains of depressed suicides. Shaw et al (1967) found lowered 5HT concentrations in the hindbrains (lower brainstem) of suicides when compared with controls, while Bourne et al (1968) found no difference in 5HT concentration, but a lowered 5HIAA concentration. Pare et al (1969) also found significantly decreased 5HT concentrations and decreased 5HIAA, but this did not reach significance. More recently Lloyd et al (1974) examined various areas of brain from depressed suicides and found significantly decreased 5HT concentrations in the lower brainstem; 5HIAA levels were essentially unaltered as compared to controls. In the higher brainstem and telencephalon, 5HT levels were normal in the suicides, whereas 5HIAA levels may have been increased in certain limbic structures, such as the mammillary bodies. Gottfries (1980), however, reviewed methodological problems of measuring post-mortem 5HT and 5HIAA, and concluded that the reduced levels found in suicide victims could be explained by a post-mortem degradation of the substances.

The mode of action of antidepressants further helps identify the biochemistry of depression. Van Praag (1981) in a review of the management of depression with 5HT precursors, considered 27 trials and concluded that in many patients there was an antidepressive effect, which gives support to the 5HT hypothesis of depression. Mendels and Frazer (1975) reviewed the literature on serotonergic activity in affective disorders, and highlighted many similar findings in mania and depression, such as low CSF tryptophan, and the both antidepressant (Coppen et al 1967; Herrington et al 1974; Fernando et al 1975) and antimanic (Prange et al 1974) properties of tryptophan. This provides indirect support to the notion of a shared indolaminergic deficiency in mania and depression, which is further strengthened by studies which demonstrated low 5HIAA in the lumbar CSF of both manic and depressed patients (Dencker et al 1966; Coppen 1972; Coppen et al 1972a). This may not be so surprising, as while there are certainly many differences in the clinical features of these 2 conditions, it is clear that the majority of manic or hypomanic patients do have significant depressive symptoms (Beigel and Murphy 1971; Kotin and Goodwin 1972).

In addition, in normal test subjects, 5-hydroxytryptophan (5HTP) administered by intravenous drip has a euphorising effect (Trimble et al 1975; Pühringer et al 1976). In patients treated with 5HTP for myoclonus, evidence of euphoria and even of hypomania has been described (van Woert et al 1977). In the majority of patients, the biochemical signs of central 5HT deficiency persist during symptom free intervals

(Coppen 1973, van Praag 1977). This seems to suggest that the suspected central 5HT deficiency is not so much a causal as a predisposing factor (van Praag and de Haan 1980).

Maas (1975) defines the group of depressives with deficient serotonergic mechanisms as "Group B", whose characteristics are normal urinary MHPG, decrements in urinary MHPG following administration of imipramine or desipramine, no response to imipramine or desipramine, no mood change with dextroamphetamine, and response to treatment with amitriptyline. Amitriptyline is a TCA which inhibits re-uptake of 5HT more markedly than that of NA (Ross and Renyi 1969; Lidbrink et al 1971). As was described earlier, Group "A" patients with low urinary MHPG do not respond to amitriptyline. It is conceivable that these less favourable results are based on the relatively slight NA-potentiating effect of amitriptyline, while the favourable effect in normal or high MHPG excretors is based on its relatively marked influence on 5HT (van Praag 1977). Early reports suggested that clomipramine may owe its clinical efficacy to its ability to inhibit 5HT uptake (Carlsson et al 1969a; Waldmeier 1976). More recently, zimelidine, a selective 5HT re-uptake inhibitor (Ögren et al 1981) has been shown to be antidepressant (Montgomery et al 1981; d'Elia et al 1981; Åberg 1981; Wålinder et al 1981).

Ågren (1980a) reported data on 33 patients who met the RDC for major depressive disorder (21 unipolar and 12 bipolar), and compared them with psychiatrically healthy patients. Lumbar CSF analyses showed HVA and 5HIAA, but not MHPG to be significantly lower than in the controls, in both unipolars and bipolars. There was a non-significant tendency for values to be lowest in the bipolar group. No firm conclusions can be drawn from this, since the controls were insufficiently defined. The author, however, felt it acceptable to identify broad syndrome groups from the results for unipolar patients. The results are interesting as they contain elements often attributed to patients with epilepsy. A high HVA syndrome would consist of demandingness, suspiciousness, terminal insomnia and distinct quality of mood; a low HVA syndrome would be characterised by initial and middle insomnia, depersonalisation and self-pity. A high MHPG syndrome would be characterised by lack of energy, overt anger, self-pity and somatic preoccupation; a low MHPG syndrome was correlated with discouragement, demandingness, subjective anger, suicidal tendencies, indecisiveness and obsessions or compulsions. A high 5HIAA syndrome is characterised by demandingness, terminal insomnia, distinct quality of mood; a low 5HIAA syndrome would simply stand for initial and middle insomnia.

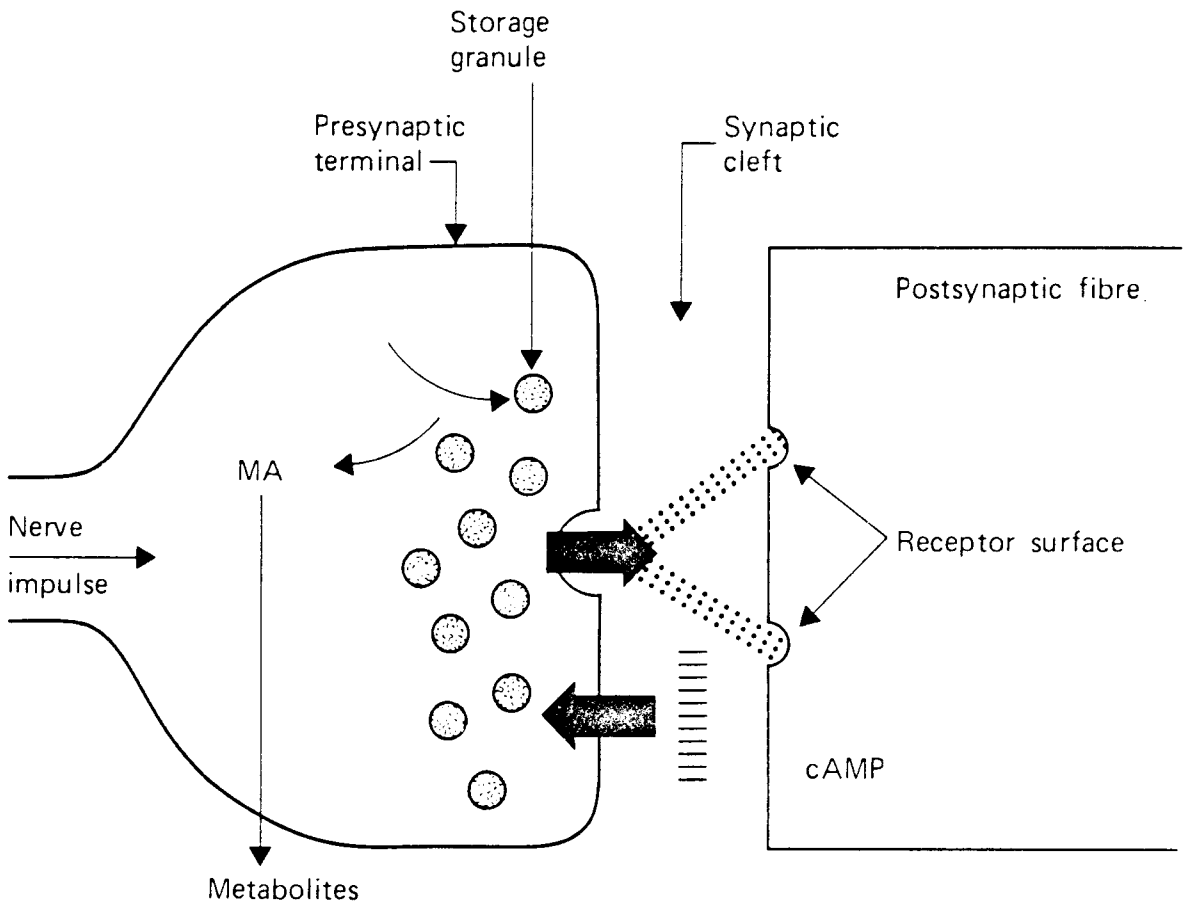


Figure 3

Model of a central aminergic synapse. The neurotransmitter stored in vesicles in terminal bouton is released into synapse as nerve action occurs. Access to receptors postsynaptically triggers initially chemical events (through cyclic AMP) and later electrical transmission. Presynaptic MAO provides a steady turnover of stored transmitter. Major "off-switch" is the amine pump (lower arrow directed presynaptically), which recaptures released transmitter. Tricyclic antidepressants block this active transport system (cross-hatched lines). *(From Hollister 1978a)*

Other results (Ågren 1980b) support earlier work of Åsberg et al (1976b), that depressives with low 5HIAA are prone to violent suicides, but, in addition, pointed out an equal, if not greater involvement of MHPG and noradrenergic systems in carrying out a death wish.

Murphy and Weiss (1972) suggested that unipolar patients may more closely fit the hypotheses that suggest a decrease in brain monoamine levels during depression (Schildkraut 1965), while bipolar illness may be due to a defect in the system that regulates amine metabolism (Bunney et al 1972). Bunney et al (1972) moreover, speculated that an increase of NA at the synaptic cleft could be implicated in the "switch" process from depression to mania.

In conclusion, it appears that some consensus is gathering on the possible role of lowered 5HT levels in both depression and mania, and elevation of catecholamines in the "switch" process from depression to mania. The relationship of catecholamines to depression, on the other hand, is the subject of controversy.

The permissive amine hypothesis

A third amine hypothesis, the so-called "permissive amine hypothesis" of affective disorders (Prange et al 1974), is perhaps a more elegant and a better summary of existing monoamine data. Briefly it holds that a central 5HT deficiency may represent a susceptibility or vulnerability to affective illness, and this predisposition may separate the depressive patient from the normal individual: hence, if catecholamine levels decrease, depression occurs (when both catecholamines and indoleamines are low) and if the catecholamines increase, it would be accompanied by mania. Carlsson et al (1969a) suggest, moreover, that blockade of 5HT re-uptake is involved in the mood-elevating action of the TCAs, with the tertiary amines such as amitriptyline being more potent, whereas the blockade of NA re-uptake promotes drive in the depressed patient which is more successfully done by the secondary amines such as desipramine, nortriptyline and protriptyline.

Ridges (1975) in her review concludes that most researchers have shown 5HIAA levels to be reduced in depression, (especially in unipolar depressives), whereas equivocal data have been obtained in studies of the catecholamine metabolites. Baldessarini (1975) critically evaluated the amine hypothesis in affective disorders, and concluded that studies of amine metabolism have not provided consistent support for the hypothesis;

it must be remembered that this review was written before much of the work on deficient serotonergic mechanisms was reported. Charney et al (1981a) make the point that relatively few studies have evaluated the effect of long-term antidepressant treatment on urinary MHPG levels in depressed patients and felt that the 10 studies reporting such data gave inconsistent results. On the other hand, they reported the effect of antidepressants, including TCAs, MAOIs and zimelidine, on CSF concentrations of 5HIAA and in 11 out of 12 studies, long term treatment consistently decreased the CSF 5HIAA level, while in only one study the results were not replicated. Investigations by several groups have generally indicated that the CSF level of 5HIAA is unchanged following repeated ECT (Nordin et al 1971; Charney et al 1981a).

Gamma aminobutyric acid (GABA)

The inhibitory neurotransmitter, GABA, has long been known to be important in epilepsy and, more recently, has been implicated in the acute psychoses, especially schizophrenia, in which there is reputed to be DA overactivity (Meldrum 1982a). The principal monoaminergic systems in the brain are under powerful GABA-ergic control: these include serotonergic neurones in the nuclei of the median raphe, the noradrenergic neurones in the locus coeruleus and the dopaminergic neurones in the substantia nigra and in the mesolimbic system (Meldrum 1982b). It is hardly surprising that GABA should be invoked in the pathogenesis of depression, where monoamine abnormalities have been suggested. In a study by Post et al (1980), GABA levels in the CSF from depressed patients were shown to be lower, but not significantly different, from normal volunteers, age and sex matched. In a similar study, Gerner and Hare (1981) found the GABA levels in the CSF significantly reduced in depressed patients. In another study, Gold et al (1980) reported CSF GABA levels significantly lower than a control neurological group. Kasa et al (1982) found the mean CSF GABA levels in depressed patients significantly lower than those of a control group. Berrettini et al (1982) measured CSF and plasma GABA in patients with bipolar affective illness, and matched controls. They found no correlation between CSF and plasma GABA, but did find the plasma GABA significantly lower in 16 euthymic, medication free, bipolar patients compared with 51 normal volunteers.

Petty and Sherman (1981), on reviewing the literature and conducting their own laboratory experiments, suggested a controlling role for GABA in the "learned helplessness" model of depression. In addition, GABA-mimetic or GABA-enhancing agents have been used in therapeutic trials in mania.

Dipropylacetamide (the amide of VPA, an anticonvulsant with similar biochemical and pharmacological properties) is reported to be effective in the treatment of bipolar affective psychoses, alone or when combined with lithium prophylactically in lithium non-responders (Lambert et al 1975). Morselli et al (1980) reported a new GABA-mimetic agent to be of value in affective illness. In a double-blind placebo study, VPA alleviated symptoms of acute mania in 4 out of 5 patients (Emrich et al 1981).

Acetylcholine (ACh)

Attention has been focussed on the possible involvement of ACh in depressive illness, particularly the complex functional balance or interaction between adrenergic and cholinergic factors (Janowsky et al 1972a). Proposed most simply, mania was hypothesised to be a syndrome due to relatively diminished central ACh activity, compared to normal or increased noradrenergic and/or dopaminergic activity; depression was proposed to be the converse (Janowsky et al 1972b). Although reserpine is generally thought to produce depression via presynaptic amine depletion, its cholinomimetic effects (Bogdanski et al 1961) may also contribute to depression. A relative excess of cholinergic function can affect mood, as both long-acting (Rowntree et al 1950; Gershon and Shaw 1961) and short-acting acetylcholinesterase inhibitors such as physostigmine (Janowsky et al 1973; Modestin et al 1973; Davis et al 1976; Davis et al 1978) have produced depression. In another study (Bowers et al 1964), normal subjects were given a potent percutaneous cholinesterase inhibitor; subjects with blood cholinesterase activity 40% below control values were reported to be significantly more depressed and anxious when compared to subjects whose cholinesterase activity was not decreased to that level. In addition, workers have reported the antimanic property of physostigmine (Carroll et al 1973a; Janowsky and Davis 1979). Choline has raised brain ACh in animals (Cohen and Wurtman 1976) and produced psychotic depression in humans (Tamminga et al 1976). Deanol, a putative ACh precursor, produced depressive symptoms in 5 out of 33 patients taking the drug for involuntary movement disorders (Casey 1979). A predisposition toward affective symptoms was suggested, as 3 of the 5 cases had prior histories of depression. The appearance of depressive symptoms in predisposed individuals is in agreement with the work of others (Davis et al 1978; Janowsky and Davis 1979).

Further evidence for the notion of an underlying predisposition comes from the finding that manic-depressive patients have significantly lower red blood cell cholinesterase activity than normal controls (Milstoc et al 1975). In uncontrolled studies, synthetic anticholinergic agents and scopolamine have been considered to have mild antidepressant action (English 1962). In addition, another anticholinergic agent, benactyzine, alone, or in combination with meprobamate, has been employed with some success in treating depression (Gordon 1967; Rickels et al 1971). Further support for the theory comes from the results of Mathew et al (1982), who reported significantly lower acetylcholinesterase levels in depressed patients when compared to controls, and, following treatment with TCAs, the levels remained low, which led the authors to conclude that a low level of the enzyme might be an index of predisposition to depression. Finally, TCAs possess central anticholinergic activity (Domenjoz and Theobald 1959).

Animal data using activity rate as a model for depression also support the proposal that depression may result from cholinergic excess. Self-stimulation (Domino and Olds 1968) and locomotor activity (Fibiger et al 1970) in rats decreased when central cholinergic activity was increased. Later, however, Fibiger et al (1971) noted that cholinomimetic agents produced initial inhibition of behaviour, followed by a phase of excitation: the anticholinesterase, physostigmine, also had a biphasic effect on behavioural arousal. Results were interpreted as indicating induction of central adrenergic activity in response to central cholinergic stimulation.

Some pharmacological evidence not supporting a role for ACh in naturally occurring mood does, however, exist, as there appears no obvious relationship between the degree of central anticholinergic activity of a given TCA and its clinical efficacy or potency (Snyder and Yamamura 1977). In addition, many antidepressants induce a change in the ACh turnover rate of various brain nuclei: amitriptyline causes no change; chlorimipramine and desipramine decrease it, while nomifensine and iprindole increase it (Robinson et al 1978a).

Alternative suggestions

Data from recent investigations have led to a major challenge of the monoamine hypothesis which does not explain all the facts in depressive illness. For example, clinically effective antidepressant drugs, such as iprindole and mianserin fail to significantly inhibit neuronal uptake

In summary, a variety of long-term, but not acute, antidepressant treatments cause a desensitisation of the cyclic AMP response to NA in brain slices from cerebral cortex and limbic forebrain. Interestingly, several studies have reported decreased values of 24 hour urinary cyclic AMP in depression (Abdulla and Hamadah 1970; Paul et al 1970; Paul et al 1971a; Sinanen et al 1975), while one (Paul et al 1971b) studied the 24 hour urinary cyclic AMP excretion during a "switch" process from depression to mania, and reported that

of NA or 5HT (Gluckman and Baum 1969; Fann et al 1972; Rosloff and Davis 1974; Coppen et al 1976; Goodlet et al 1977; Zis and Goodwin 1979; Sandler et al 1980), while an effective uptake blocker such as femoxitine (Ghose et al 1977) is not useful in the treatment of depression. In addition, the time course of drug effects on amine availability and clinical improvement is not consistent. While TCA blockade of re-uptake and MAOI inhibition of amine catabolism occur rapidly after a single dose (Iversen and MacKay 1979), clinical response to these agents usually requires 2 or more weeks to become evident (Oswald et al 1972; Klein et al 1980). Against this background there has been much research into additional modes of action of antidepressant drugs, and reconsideration of the abnormalities underlying depression.

Cyclic AMP

Cyclic AMP has been implicated in the molecular basis of antidepressant action since it participates in synaptic transmission. Noradrenaline and other neurotransmitters (the first messengers) combine with post-synaptic receptors on the outer surface of the cell membrane, thus activating the enzyme adenylcyclase on the inner surface of the cell membrane. This enzyme increases the intracellular cyclic AMP (the second messenger) which induces the physiological response (Laurence and Bennett 1980). The mechanism whereby antidepressant drugs reduce NA-stimulated cyclic AMP accumulation is not understood fully. Most TCAs, either directly or through their metabolites, potentially antagonise the high affinity uptake system for NA in the brain; thus, these drugs and the MAOIs which block NA degradation, may act to enhance the synaptic availability of NA and thereby promote receptor desensitisation. This hypothesis is consistent with reports that long-term manipulations which increase or decrease NA receptor stimulation cause compensatory changes in the sensitivity of the cyclic AMP response to NA in vitro (Charney et al 1981a). A major difficulty in interpreting alterations in NA stimulated cyclic AMP accumulation arises from the incompletely understood

As early as 1968, it was suggested that the primary abnormality in depression in man was at the adrenergic receptor level (Rosenblatt et al 1968). Aprison and colleagues (Aprison and Hintgen 1981) suggested that unipolar depression in humans involves hypersensitive postsynaptic receptors. Charney et al (1981b) confirmed the studies previously conducted in laboratory animals by using clonidine hydrochloride, an α2-agonist, to evaluate its effects on plasma levels of the NA metabolite MHPG, and on the blood pressure (BP) of 10 depressed patients before and during long-term desipramine treatment. Long-term desipramine treatment significantly decreased the effects of clonidine on BP, indicating that during desipramine treatment α2-adrenergic receptors had become subsensitive. In addition, plasma MHPG levels were significantly reduced during long-term desipramine treatment. Similar results have been reported by Checkley et al (1981). The finding that long-term desipramine administration decreased the hypotensive action of clonidine is consistent with a decrease in α 2-adrenergic receptor sensitivity (Sharma et al 1978; Rockhold and Caldwell 1980). Clonidine normally induces a short-term decrement in BP that is thought to be mediated by its actions as an agonist on CNS presynaptic α 2-adrenergic autoreceptors. The coincidence of timing of such a subsensitisation and the onset of clinical response to antidepressants raise the possibility that the α 2-adrenergic desensitisation may play an important role in the clinical efficacy of antidepressants (Siever et al 1981). Several workers implicate presynaptic α 2-adrenergic receptor blockade with the therapeutic effects of mianserin (Baumann and Maitre 1977; Robson et al 1978; Tang et al 1979) and trazodone (van Zwieten 1977).

Garcia-Sevilla et al (1981) found significantly more platelet α 2-adrenergic receptors in drug free depressed patients than in a group of normal controls: treatment with TCAs produced a significant fall in the numbers of α 2-receptors. This work supports the hypothesis that in depression there is a "supersensitivity" of α 2-adrenergic receptors and that the clinical efficacy of the TCAs is associated with a decrease in the number of these receptors. Wood and Coppen (1982) reported that drug free, depressed patients, had a significantly reduced number of binding sites when compared with a normal control group. They pointed out that the discrepancy between their results and those of Garcia-Sevilla et al (1981) may be explained by a difference either in diagnostic selection or in pharmacological method.

Although presynaptic α 2-adrenergic receptors are the most implicated in depressive illness at present, reports show that many other receptors may also be involved. Fairly consistent alterations in postsynaptic α 1-adrenergic receptor sensitivity have been induced by a wide variety of antidepressants (Maj et al 1979; Menkes et al 1980; Snyder 1980; Tang and Seeman 1980). Svensson et al (1981) make the point that activation of postsynaptic α 1-receptors, secondary to increased synaptic availability of NA, may cause alleviation of psychomotor retardation by the administration of TCAs in depressive states. On the other hand, the pronounced sedative effects of some TCAs seem correlated with their α 1-receptor blocking properties (U'Prichard et al 1978). The development of β adrenergic receptor decrease or subsensitivity after long-term treatment with some antidepressants has been reported by several groups (Bannerjee et al 1977; Sarai et al 1978; Clements-Jewery 1978; Maggi et al 1980; Peroutka and Snyder 1980). Conversely, reserpine, a drug known to cause a depressive syndrome in man, causes β -adrenoceptor supersensitivity (Sulser and Vetulani 1977). Antidepressant drugs also possess potent activities on many other receptors including 5HT receptors (De Montigny and Aghajanian 1978; Maggi et al 1980; Peroutka and Snyder 1980; Tang and Seeman 1980; Fillion and Fillion 1981; Takahashi et al 1981), DA receptors (Serra et al 1979; Menkes et al 1980; Antelman and Chiodo 1981), ACh receptors (Richelson 1979; Snyder and Yamamura 1977), histamine H_1 receptors (Psychoyos 1978; Richelson 1979; Snyder 1980; Taylor and Richelson 1980; Tran et al 1981) and histamine H_2 receptors (Green and Maayani 1977; Rehavi and Sokolovsky 1978). It should be noted that, in contrast to the effects of antidepressants which cause subsensitivity of receptors, repeated neuroleptic treatment induces a supersensitivity of DA receptors (Nowycky and Roth 1977; Galager et al 1978).

Other abnormalities encountered in depression

Many other abnormalities have been reported in depression. These include: abnormalities of HLA antigens, especially increases of A_3, B_7 and B_{16} (Shapiro et al 1976; 1977; Stein et al 1980), although the findings were not confirmed by Bennahum et al (1975); electrolyte disturbances, especially residual sodium which includes intracellular sodium, was increased during depression and decreased on recovery (Coppen and Shaw 1963; Naylor et al 1971): when the data from experiments were pooled, results showed a significant reduction in mean transfer rate of sodium in depression, and an increase associated with recovery (Carroll 1972); several other electrolyte abnormalities have been described (Hesketh et al 1977; Baer

et al 1970); high erythrocyte COMT activity (Gershon and Jonas 1975) and low erythrocyte COMT activity (Cohn et al 1970) have also been reported. Abnormalities of cortisol metabolism, which will be reviewed in the section on the DST, have also been noted. It is of interest that cortisol and adrenocorticotrophic hormone (ACTH) have effects on sodium metabolism (Wasserman et al 1965).

Currently, peptides such as thyrotrophin releasing hormone (TRH), luteinising hormone (LH), PRL, β endorphins and substance P are exciting much interest. Increased endorphin levels have been reported in depression (Terenius et al 1977) and β endorphins have been given, in at least one clinical investigation, as antidepressants (Kline et al 1977). Enkephalins, too, (Pollard et al 1977) appear to alter central monoamine function.

Folic Acid (FA)

It is of interest that low serum FA has been reported in depressed patients (Gough et al 1963; Forshaw 1965; Reynolds et al 1966b; Carney 1967; Reynolds et al 1970; Botez et al 1976; Thornton 1977; Trimble et al 1980), as this has been found in epileptics, as will be discussed. Trimble et al (1980) reviewed 19 studies of the relationship of FA to psychiatric illness. In 17 out of 18 the serum FA was reduced: in 3 out of 3 the rbc FA was reduced. A relationship between FA deficiency and higher scores on depression rating scales has been reported (Reynolds et al 1970; Ghadirian et al 1980). Reynolds' (1976) view is that "severe folate deficiency gradually leads to apathy, depression, social withdrawal and ultimately dementia". Contributory factors to low FA in psychiatric patients may be due to drug treatment, including antidepressants in 79% physical illness in 18.6%, and malnutrition in 22.1% (Carney and Sheffield 1970): no such extrinsic factors were found in 25%. Other authors (Ibbotson et al 1967; Reynolds et al 1970; Reynolds 1976) also emphasise the dietary importance of FA deficiency in depression and psychotic illness.

In conclusion, the following statement from Coppen in 1972 can be quoted: "I should like to stress from the outset my view that the chemical pathology of the affective disorders is probably very complex - involving not only the biogenic amines, but probably also other abnormalities". This is borne out by the review.

1.6. Treatment of Depression

For decades, anxiety, agitation, insomnia and other related features of depression were treated by barbiturates, chloral hydrate and bromides (Spencer 1977). In the late 1930's, amphetamines were used for treating depression, soon after their introduction into medical practice. Meduna introduced a method of inducing convulsions by the injection of metrazol, initially used in schizophrenia; Bennett soon discovered that convulsive therapy was of more benefit in manic-depressive psychosis (Alexander 1953). ECT was introduced in 1938 for treating selected cases of severe depression (Cerletti and Bini 1938). Cade (1949) introduced lithium salts for the treatment of chronic or recurrent manic episodes in the course of manic-depressive illness. Adverse effects such as paranoid psychoses caused by amphetamines, and fear of the abuse of ECT, led to the evolution of that group of drugs known nowadays as antidepressants (Blackwell 1981a).

In 1957, imipramine (the archetype antidepressant and first TCA) and iproniazid (the first MAOI) were introduced almost simultaneously. Iproniazid was originally studied in 1951 by Fox for treatment against tuberculosis, and it was observed that the patients became euphoric, and this effect on their mental state exceeded the improvement of their tuberculosis; the beneficial effects were attributed to central stimulant properties (Davis 1958). Zeller et al (1952) showed that iproniazid was an inhibitor of mammalian monoamine oxidase. Kline (1958) carried out successful trials with iproniazid in depressed patients, after which the drug was introduced as an antidepressant. Kuhn noticed an improvement in the depressive symptomatology of schizophrenics receiving imipramine, and after a carefully conducted study of a large number of patients, its antidepressant properties were confirmed and imipramine was officially introduced as an antidepressant, the first of the TCA group (Kuhn 1958). Commonly used antidepressants, and some of their properties are shown in Table 4.

That the TCAs are useful in certain types of depressive illness is well established. Morris and Beck (1974) reviewed 146 controlled double blind studies on medications used as antidepressants, and reported results statistically significant only if they met the probability level of .05 or better. Results showed TCAs to be significantly more effective than a placebo in 61 of 93 group comparisons. No study reported a placebo as more effective than a TCA. Of the TCAs studied, amitriptyline, its

Table 4 **COMMON ANTIDEPRESSANTS** *(Grouping adapted from Spencer 1977; Silverstone & Turner 1978)*

GROUP	Sub Group	Generic Name	Proprietary Names	Year introduced to UK (12)	Usual daily dose (mg)	Onset of Action	Reported Plasma Half Life (hrs)	Sedative / Stimulant	Inhibition of mono amine uptake
1 Monoamine reuptake inhibitors (MARI)	i) Bicyclic	Viloxazine	Vivalan	1974	100–300 (4)	5–10 days (13)	2–5 (7)	Sedative < Amitrip (1)	NA (23)
		Zimelidine (29)	Zelmid	1982	50–300 (7)	2 weeks (12)	6.5 metabolite 17 (12)	Non-sedative (12)	5-HT (24)
	ii) Tricyclics	Amitriptyline	Domical Elavil Endep Lentizol Tryptanol Tryptizol Saroten	1961	75–200 (4)	10–30 days (3)	31–46 (7)	Sedative (2)	5-HT potent (4) NA medium (4) Hist medium (26)
		Butriptyline	Evadyne	1975	50–150 (4)	7–14 days (20)	65–135 (19)	Sedative (1)	DA (25)
		Clomipramine (Chlorimipramine)	Anafranil	1970	50–150 (4)	i.v. 5 days (3)	22–84 (7)	Sedative (1)	5-HT potent (26, 29) NA (26, 29)
		Desipramine	Norpramine Pertofran	1962	75–200 (4)	2–7 days (3)	14–62 (7)	Mildly sedative (2)	NA potent (4, 27) 5-HT weak (4, 27)
		Dothiepin	Prothiaden	1969	75–150 (4)	7–10 days (13)	24 (12) 50 for active metabolite (12)	Sedative ≡ to Amitrip (1)	NA (22) Hist potent (22)
		Doxepin	Adapin Sinequan	1969	75–150 (4)	few days to >2 weeks (3)	8–24 (7) metabolite 33–81 (7)	Sedative ≡ to Amitrip (2)	NA potent (13) 5-HT (13) Hist (13)
		Imipramine	Berkomine Imavate Janimine Praminil Presamine Tofranil	1959	75–200 (4)	up to 4 weeks (3)	9–20 (7)	Sedative (2) < Amitrip	NA medium (4, 26) 5-HT potent (4)
		Lofepramine	Deprimil Gamanil Gamonil	1983	140–210 (12)	2–5 days (12)	1.5–5 (12)	Non sedative (12)	NA (12)
		Nortriptyline	Allegron Aventyl Pamelor	1963	75–200 (4)	3–5 days (12)	18–93 (7)	Sedative < Amitrip (2)	NA moderate (15) 5-HT slight (15)
		Protriptyline	Concordin Triptil Vivactil	1967	15–60 (4)	Within 1 week (3)	54–198 (7)	Non sedative (2)	NA potent (4) 5-HT weak (4)
		Trimipramine	Surmontil	1966	50–100 (4)	7–10 days (13)	Unknown (12)	Sedative > Amitrip (1)	Hist potent (22) 5-HT (22)
	iii) Tricyclic related	Dibenzepin	Noveril	1970	240–480 (4)	10–14 days (3)	4 (3)	Sedative (4)	
		Iprindole	Prondol	1968	45–90 (4)	1–2 weeks (3)	Unknown (12)	Sedative < Amitrip (1)	No conspicuous pharmacological effect (23)
		Opipramol	Insidon	1971	100–300 (3)	10 days (3)	–	Sedative (3)	
	iv) Tetracyclics	Maprotiline	Ludiomil	1975	50–150 (4)	1–2 weeks (3)	52 (3)	Sedative < Amitrip (1)	NA potent (26, 29) Hist (26)
		Mianserin	Bolvidon Lantanon Norval Tolvin	1976	20–60 (4)	1–2 weeks (18)	10–17 (7)	Sedative (9)	Hist (23, 29)

continued.....

GROUP	Sub Group	Generic Name	Proprietary Names	Year introduced to UK (12)	Usual daily dose (mg)	Onset of Action	Reported Plasma Half Life (hrs)	Sedative / Stimulant	Inhibition of mono amine uptake
2 Monoamine oxidase inhibitors (MAOI)	i) **Hydrazines** a) with acute stimulant effects	Iproniazid	Marsilid	1957	50 - 75 (4)	2 - 3 weeks (12)	Unknown (12)	Stimulant (10)	Inhibit mono amine oxidase activity (1)
		Isocarboxazid	Marplan	1960	20 - 40 (4)	1 - 4 weeks (13)	Unknown (12)	Stimulant (10)	
		Phenelzine	Nardil	1959	30 - 60 (4)			Stimulant (10)	
	b) without acute stimulant effects	Nialamide	Niamid	1959	50 - 150 (4)	14 days - 3 weeks (1)	–	Non stimulant (10)	
	ii) **Non-Hydrazines** a) with acute stimulant effects	Tranylcypromine	Parnate	1960	10 - 30 (1)	7 days - 3 weeks (1)	12 – 24 (12)	Stimulant (10)	
	b) without acute stimulant effects	Pargyline	Eutonyl		25 - 50 (3)		–	Non stimulant (10)	
3 Naturally occuring agents	i) Amino Acid precursors of transmitters	L Tryptophan	Optimax Pacitron	1971	3000 – 6000 (1)	3 – 4 weeks (3)	15.8 (3)	Sedative (3)	5-HT Precursor (4)
	ii) Lithium salts		Camcolit Liskonum Priadel	1964	250 - 2000 (1)	Acute 3 – 7 days mania 1 - 2 wks (Depression) Prophylaxis up to 12 months (13, 21)	10 – 24 (12)	Non sedative (5)	
4 Amphetamine related sympathomimetic agents	i) Releasers of non granular amine stores	(+) Amphetamine (dexamphetamine)	Dexedrine		5 - 60 (1)	Uncertain (12)	12 (12)	Stimulant (1)	
	ii) Releasers of granular and non granular amine stores	Methylphenidate	Ritalin	1955	20 - 30 (1)	15 - 45 mins (12)	2 - 3.5 (12)	Stimulant (1)	
5 Miscellaneous		Flupenthixol	Fluanxol	1973	2 - 3 (1) 1 - 2 (14)	3 days (14)	24 - 48 (16)	Non sedative	DA antagonist (14)
		Nomifensine	Alival Merital	1977	50 - 150 (4)	7 - 10 days (13)	2 (6)	Mild stimulant (17)	DA (10, 23) 5-HT (23) NA (28, 29)
		Tofenacin	Elamol	1971	240 (3)	4 - 7 days (8)	7.4 (12)	Unapplicable	
		Trazodone	Desyrel Molipaxin	1980	50 - 600 (7)	10 - 30 days (11)	6.3 (11)	Sedative (11)	5-HT (23, 29)

Note: The numbered references are shown in Table 5

> *more than*

< *less than*

≈ *similar to*

TABLE 5: REFERENCES FOR TABLE 4

1. BNF 1982
2. Hollister 1980
3. Martindale 1977
4. Silverstone and Turner 1978
5. Baldessarini 1980
6. Hanks 1977
7. Hollister 1981a
8. Wall and Wright 1973
9. Perry et al 1978
10. Forrest et al 1977
11. Brogden et al 1981
12. Pharmaceutical companies - personal communication 1982, 1983
13. Data Sheet Compendium 1981/1982
14. Robertson and Trimble 1981
15. Hollister 1978b
16. Jørgensen 1978
17. Blackwell 1981a
18. Smith et al 1978
19. Cameron et al 1974
20. Brodie et al 1978; Suy 1976
21. Worrall et al 1981; Khan 1981
22. Manufacturers literature
23. Maj 1981
24. Åsberg and Bertilsson 1979
25. Blackwell 1981a
26. Trimble 1981
27. Ross and Renyi 1969; Carlsson et al 1969a; 1969b
28. Klein et al 1980
29. Hollister 1981b

derivatives (nortriptyline and protriptyline) and a chemically similar drug (doxepin) showed the most impressive efficacy, with 27 of 37 comparisons (72.4%) reporting results superior to those with placebo. Amitriptyline alone was superior to placebo in 14 out of 20 studies (70%). Today amitriptyline is the most widely prescribed antidepressant (Blackwell 1981a). Bielski and Friedel (1976) critically reviewed all the prospective double blind controlled studies which have evaluated the prediction of response to amitriptyline and imipramine in depressed patients. They found that predictors of positive response to the 2 drugs were as follows: upper socioeconomic class, insidious onset, anorexia, weight loss, middle and late insomnia, and psychomotor disturbance. The predictors of poor response were: neurotic, hypochondriacal and hysterical traits, multiple prior episodes, and delusions. In addition, pretreatment low urinary MHPG was suggested as a positive predictor for imipramine and a negative predictor for amitriptyline, while the reverse was true for high urinary MHPG.Rama Rao and Coppen (1979) investigated the classification of depression and response to amitriptyline therapy by rating 54 patients suffering from primary depressive illness on the Newcastle diagnostic scale. Patients with a Newcastle score of 4 to 8 showed the best response to amitriptyline. Patients with low scores responded poorly, while Robinson et al (1974) suggested that this group may do well on MAOIs. Patients with high scores of 9 to 11, representing those with marked endogenous features, also responded poorly. This group is similar to the "delusional depressives" who were reported to respond poorly to TCA therapy but well to ECT (Glassman et al 1975).

Several studies have attempted to discover whether the continued administration of TCAs to patients, after they have recovered from a depressive illness which responded to treatment with ECT, imipramine or amitriptyline, is associated with a lower rate of recurrence than giving no treatment, and in all studies the continuation therapy with TCAs prevented relapse (Mindham 1982).

All the TCAs produce similar unwanted effects which vary in severity and type between the different preparations. The most often reported side effects are due to the anticholinergic properties of the compounds. It has been demonstrated that the severity of the unwanted effects of nortriptyline are directly related to plasma levels of the drug (Åsberg et al 1970; Ziegler et al 1978). Side effects often noted are dryness of the mouth, difficulty with visual accommodation, difficulty in initiating micturition, constipation, palpitations and postural hypotension (Mindham 1982). Åsberg et al (1970) point out that some side effects attributed to

the drugs, such as dryness of the mouth, constipation and fatigue, are, however, also well recognised symptoms of depression. Retention of urine, and paralytic ileus are occasionally seen (Mindham 1982). The major area of concern about the TCAs has been their severe toxic effects on the cardiovascular system, both in therapeutic amounts and overdose (Blackwell 1981a). The TCAs may precipitate excitement or even hypomania (Leyberg and Denmark 1959), but these complications are rare. Dyskinesias have also been associated with the TCAs (Fann et al 1976). Skin rashes occur occasionally and agranulocytosis is rare (Mindham 1982).

The fact that TCAs lower the seizure threshold has long been evident from their animal pharmacology (Blackwell 1981a), but more recently their tendency to produce seizures is of concern. Table 16 (page 111) shows a table of convulsions reported to the Committee on the Safety of Medicines (CSM) in Britain until 1981. Amitriptyline (the most widely prescribed antidepressant) was associated with 13% of the seizures but 34.2% of prescriptions (Blackwell 1981a).

Whether or not TCAs induce hepatic enzymes is controversial. Measurement of antipyrine half-life is a method used to assess drug-metabolising capacity in man (O'Malley et al 1971). O'Malley et al (1973) measured the plasma antipyrine half-lives in 30 adult subjects before, and after 7 and 28 days treatment with 1 of 5 TCAs. Overall, considering the 5 antidepressants together, there was a small but significant reduction in the antipyrine half-life after both periods of treatment. In 4 subjects studied, increased urinary output of 6β-hydroxycortisol following chronic nortriptyline treatment provided further evidence of a stimulatory effect of TCAs on drug metabolism. The authors also reported on a separate study in which the induction effect of TCAs was found to be much less marked than that with amylobarbitone. These results are in contrast with those of Vesell et al (1970) who found one TCA, nortriptyline, to have an inhibitory effect on drug metabolism, as it prolonged the plasma half-life of antipyrine. There have been more studies on the effects of TCAs on drug metabolism in animals. It is generally held from acute studies that the TCAs exert an acute inhibitory effect on the microsomal enzymes involved in drug metabolism (Kato et al 1964; Mitchell et al 1970; Shand and Oates 1971). Reports on chronic effects of the TCAs are conflicting, with the only 2 studies performed giving opposite results, one showing inhibition and the other increasing the rate of metabolism of the 2 substrates (O'Malley et al 1973).

Viloxazine, chemically related to propranolol, is reported to have the potency of imipramine, and seems comparable to other antidepressants, but nausea occurring in almost 20% of cases in one series, is common (Mindham 1982).

Zimelidine is a newcomer and was reported to have virtually no side effects (Astra 1982). However, there have been reports of severe headaches and disturbed liver function during treatment with zimelidine (Syvälahti et al 1979; Sommerville et al 1982).

The 2 tetracyclics, maprotiline and mianserin, were recently introduced (1975 and 1976 respectively). Looking at Table 16 (page 111), it can be seen that maprotiline has been implicated in 117 (36%) of cases of convulsions compared to its 3.6% share of antidepressant prescriptions and only 8 years on the market; 25% of all patients who overdose with maprotiline experience convulsions. Mianserin, only 7 years on the market, accounts for 12% of reported antidepressant-related convulsions and 5.8% of antidepressant use (Blackwell 1981b; Edwards 1979; Edwards and Glen-Bott 1983). Relatively speaking therefore these 2 antidepressants are the most toxic when considering seizures as side effects. Mianserin has however, a well established efficacy, with fewer anticholinergic side effects and less cardiotoxicity than amitriptyline (Brogden et al 1978; Klein et al 1980). Recently there have been reports of blood dyscrasias attributed to mianserin (Curson and Hale 1979; McHarg and McHarg 1979; Clink and Shaw 1982; Page 1982) as well as 19 reports of arthritis or arthralgia on the Adverse Reactions Register (CSM 1982).

Nomifensine is a tetrahydro-isoquinoline derivative that appears to strongly inhibit the re-uptake of DA, as well as NA but only weakly that of 5HT (Mindham 1982). The majority of data suggests that it may have mild stimulant properties, with less weight gain and more effect on retardation than the TCAs; it is also reported to have less anti-cholinergic effects than the TCAs (Blackwell 1981b). Nineteen orthodox controlled trials outside Britain, in which about 400 patients have been treated with nomifensine, have shown it to have an effect comparable with that of other standard antidepressants (Habermann 1977). It has also been shown to be superior to placebo (Taeuber 1977). Generally it is accepted that as an antidepressant it appears to be equally efficaceous as the TCAs and their analogues (Mindham 1982). On account of its dopaminergic effect it has been used in the treatment of Parkinson's disease, but with varying results.

No seizures have been reported with nomifensine (Edwards and Glen-Bott 1983), although it has been marketed for 5 years. It is interesting that butriptyline, also never having caused convulsions (Edwards and Glen-Bott 1983), is also reported to have potent DA effects (Blackwell 1981a). In addition, in experimental models of epilepsy, nomifensine does not alter the seizure threshold, in contrast to TCAs, which lower it; it was concluded that the dopaminergic mechanisms were probably responsible for the differing effect (Trimble et al 1977).

The MAOIs were introduced early in the modern era of psychopharmacology, but their precise utility has remained undetermined and is controversial (Nies and Robinson 1982). The MAOIs are divided into the hydrazines and non-hydrazines (see Table 4). Further subdivision into selective inhibitors (of MAO-A or MAO-B) and non-selective inhibitors is possible, but the clinical significance of this is not yet known (Nies and Robinson 1982). Their peak of popularity was in the early 1960's, followed by 10 years of relative neglect, but there is now increasing interest in their use (Blackwell 1981a). Their most undesirable effect is the "wine and cheese syndrome" which occurs when the patient eats amine-containing foodstuffs such as chianti wine, cheese, banana peel, pickled herring, yeast extracts, broad beans and caviar. Symptoms indicating an untoward reaction are unexpected drowsiness or sudden, severe headache. They also interact with other drugs, including the TCAs. However, with care, the MAOIs can be used with the TCAs (Schuckit et al 1971; Spiker and Pugh 1976). Few convulsions have been reported with the MAOIs (see Table 16, page 111) although they have been in use for over 20 years. Their most appropriate use is in phobic states, agorophobia, depression in which anxiety is a major presenting feature of the illness, and in chronic atypical and non-endogenous depressions (Iversen and Mackay 1979; Blackwell 1981a; Nies and Robinson 1982).

Amoxapine (Demolox), a new dibenzoxapine compound, resembles imipramine in structural and pharmacological properties. It has been used in both open and double-blind trials in South Africa and the USA, but not in Britain. It has been found to have antidepressant qualities, improvement being evident within one to 2 weeks, and to have minimal side effects (Ota et al 1972; Sathananthan et al 1973; Smith 1975; van Wyk and Louw 1982). Amoxapine has caused convulsions in 3 patients who took an overdose (Bock et al 1982; Golberg and Spector 1982, cited by Bock et al 1982).

In addition to traditional antidepressants, neuroleptics have been used in depression. Robertson and Trimble (1982) reviewed the literature from 1958 to 1981 on the use of major tranquillisers as antidepressants, and 34 double-blind trials evaluating this were found. Results suggested that some neuroleptics have antidepressant properties, although most studies were conducted on mixed anxiety-depressive states. Advantages over the TCAs were the early onset of action and relative lack of side effects.

Various forms of psychotherapy may be used in the treatment of depression, either alone or in combination with medications.

1.7. The Dexamethasone Suppression Test (DST)

In the late 1950's and early 1960's there were reports of elevated plasma cortisol in depressed patients (Board et al 1957; Gibbons and McHugh 1962; Lingjaerde 1964). Gibbons (1964) confirmed these findings and found that, not only were there elevated cortisol secretion rates before treatment, but that they were higher in the more severely depressed patients; moreover, the relief of depression was accompanied by a significant decrease in cortisol secretion rate. Sachar et al (1973) described the cortisol secretion of 6 psychotically depressed patients and 8 normal persons, and showed that the depressives, while ill, secreted substantially more cortisol, that there was a disruption of the diurnal variation of cortisol secretion, and that after treatment, the patients' secretory patterns normalised. In contrast, a few authors reported that depressed patients have slight or no abnormalities in plasma cortisol levels (Shopsin and Gershon 1971). Reviews (Carroll et al 1976a; Coppen 1976) discuss the findings of cortisol values in depression: the prevailing opinion is that a subgroup of depressed patients hypersecrete cortisol. Swigar et al (1979) monitored morning and evening plasma cortisol levels in 123 psychiatric patients with a variety of diagnoses. Morning cortisol elevation was found in 33% of patients and was not associated with any particular diagnostic category. Evening cortisol elevation occurred in 85% of subjects, and was significantly higher in those with unipolar depression, organic brain syndrome and those who abused alcohol, regardless of the diagnosis.

A few workers have measured cortisol in the CSF of depressed patients, and although the majority have found it to be high, some have found normal values, and others low values (Carroll et al 1976a; Träskman et al 1980).

In 1960 Liddle formalised the DST as a diagnostic tool in Cushings Syndrome, to distinguish the raised cortisol production found in the condition from that found in others. Under normal circumstances the adrenocortical secretion of cortisol is governed by the amount of ACTH secreted by the pituitary. Since one of the characteristic actions of cortisol is suppression of ACTH secretion, the ACTH-cortisol relationship can be seen as a mechanism in which cortisol levels tend to be self-regulating; an increase in cortisol initiates a sequence of events which ultimately restrains further secretion of cortisol. After the initial report by Liddle (1960) several variants of the test followed. Nichols et al (1965) observed that single doses of dexamethasone have their greatest effect in suppressing plasma cortisol levels when given at night. Subsequent to this finding, the single dose "overnight" DST was described by several authors (Nugent et al 1965; McHardy-Young et al 1967). A single oral dose of 1mg or 2mg of dexamethasone was administered to the patients between 11pm and midnight, and a normal response, ie. suppression of plasma cortisol over the following 24 hours, ruled out the presence of Cushing's Disease with a high degree of confidence. Nugent et al (1965) reported that in acutely ill patients and persons taking oestrogens, false positive results could be obtained.

Suppression tests were then introduced into psychiatry. Persky (1957) was among the first to note that anxious patients tended not to suppress cortisol after a suppression test using hydrocortisone. Stokes (1966), the first to use the overnight DST in psychiatric patients (although details of diagnosis were not given), reported that the patients' cortisol levels post DST were significantly greater than normal controls, and not significantly different from patients with Cushing's Syndrome.

Gibbons and Fahy (1966) were the first to report on the DST in endogenously depressed patients. They gave the patients and control subjects an intramuscular injection of dexamethasone at 2pm. Over the following 3 hours, similar suppression of plasma 11-hydroxycorticosteroids were observed in both groups, and the authors concluded that the acute suppressive action of dexamethasone was not affected in depressed patients. The patients, however, tended to have higher corticosteroid levels both before and after the experiment.

Independently, Butler and Besser (1968) and Carroll et al (1968), using the DST in patients with endogenous depression, described non-suppression of cortisol post DST. Others studied the DST and found generally consistent results: about 46% of melancholic or endogenously depressed patients had abnormal DST results, in that they did not suppress cortisol (Carroll 1977). Carroll and associates (1976b; 1976c) improved the DST procedure. From the results of 48 hour venous catheter studies they concluded that the depressed patients had a more subtle hypothalamic-pituitary-adrenal cortex (HPA) disturbance than patients with Cushing's Disease. They showed that a fair proportion of depressed patients had normally suppressed plasma cortisol concentrations in the early morning, but that they escaped from suppression later in the day. Normal people, in contrast, remained suppressed for at least 24 hours after an overnight dose of dexamethasone. These findings led to new procedures for the DST, in as much as blood samples were taken at 0800 hrs, 1600 hrs, and 2300 hrs, and an elevated plasma cortisol level in any of the 3 indicated disinhibition of the HPA system. Carroll et al (1976c) then suggested that, as patients with non-endogenous depression had normal DST results, the test might be useful for diagnosing endogenous depression or melancholia.

Carroll (1982) reviewed and summarised data from 10 recent studies involving over 550 depressed patients and a similar number of non-depressed controls, and found good agreement of results. There was high specificity (ie. the proportion of non-depressed patients with normal tests), the average figure being 96%. The sensitivity of the test (ie. the proportion of all depressed patients with abnormal tests) ranged from 24% to 100%, with an average of 45%. It was pointed out that the variation in sensitivity could have been due to several factors, including different dosages of dexamethasone, varying levels of plasma cortisol concentration judged to be abnormal, and differing schedules of blood sampling.

Carroll (1982) suggested a standardised test which involved giving 1mg of dexamethasone orally at 2300 hrs, with blood sampling at 1600 hrs and 2300 hrs the next day. A plasma cortisol of $> 5\mu g/dl$ (138nm/L) in either sample was regarded abnormal. Rothschild et al (1982) found that oral administration of 1mg dexamethasone at 2300 hrs, followed by blood sampling at 1600 hrs the following day gave satisfactory results. Carroll et al (1981a) have demonstrated that of the 3 blood samples, the 1600 hrs/4pm gave the best results, in that 78% of all the positive test results were

detected by that sample. In addition, they showed that the test was not influenced by most psychotropic medication. Their advised medical exclusion criteria are shown in Table 6.

TABLE 6: MEDICAL EXCLUSION CRITERIA FOR THE DST

(From Carroll et al 1981a)

False Positive Tests

Pregnancy; high dose oestrogens
Cushing's Disease or Syndrome
Severe weight loss; malnutrition; anorexia nervosa (weight < 80% of ideal weight)
Hepatic enzyme induction (phenytoin sodium, barbiturates, meprobamate)
Uncontrolled diabetes mellitus
Major physical illness; trauma; fever; dehydration; nausea
Temporal lobe epilepsy (possible)
Reserpine and narcotics (possible)
Acute withdrawal from alcohol

False Negative Tests

Addisons Disease; corticosteroid therapy; hypopituitarism
High dose benzodiazepines (>25mg/day of diazepam)

Uncertain Exclusion Criteria

Other endocrine disease
Spironolactone

It is important to know that a normal suppression response does not necessarily exclude the diagnosis of melancholia in an individual patient, as there are a notable proportion of "false-negatives" (about 50%) in unipolar endogenous depression (Carroll et al 1976c; Gold and Pottash 1981); on the other hand, "false-positives" are exceedingly rare (Gold and Pottash 1981).

It may be said that the lack of plasma cortisol suppression is a method of confirming the presence of a major depression (Gold and Pottash 1981). In addition, a change in response to the DST may also be a guide to treatment. An abnormal response appears to be a physiological marker for active major depressive disease; if treatment is successful, the response returns to normal, and patients whose DST fail to normalise may have incomplete resolution of their underlying depressive process (Carroll et al 1976b; Greden et al 1980; Gold and Pottash 1981).

Early investigators (Sachar et al 1970) felt that HPA dysfunction was a reflection of the non-specific breakdown of psychological defence mechanisms ie. the psychosis itself. Later studies (Sachar et al 1973) found that the abnormal HPA function was not simply a result of non-specific stress, but reflected the depressive syndrome itself. Although Carroll and associates have produced much of the data on the DST, its use as a diagnostic tool for depression, and not just psychosis, has been confirmed by other centres (Brown et al 1979; Schlesser et al 1980). Rothschild et al (1982) confirmed previous work by demonstrating that post DST plasma cortisol levels were significantly higher for psychotic unipolar major depressives than for psychotic bipolar depressives, psychotic schizophrenics, "atypical" psychotics and controls. Mendlewicz et al (1982b) found non-suppression in both unipolar and bipolar depressives; however, they found non-suppression in 81% of psychotic depressives but in only 37% of non-psychotic depressives. Patients with secondary depression suppressed normally. Neither age, sex, severity of depression nor benzodiazepines influenced the results. There was, in addition, no association between cortisol non-suppression and any genetic subgroup of affective disorder. Others (Brown and Shuey 1980; Schlesser et al 1980) have also reported normal suppression in patients with secondary depressive illness.

In addition, the DST has been shown to have some special relationships with aspects of depressive illness. Patients who show escape from suppression are more likely to respond to TCAs (Brown et al 1979); some have reported an association between severity of depression and resistance to suppression (Carroll et al 1968; Brown et al 1979), while Carroll and Davies (1970) found no such association with severity, but reported a correlation between agitation and non-suppression. Coppen et al (1983) and Holden (1983) found significant associations between non-suppression and endogenicity of depression as measured by the Newcastle Diagnostic Scale.

The DST has been used with varying results in patients with other psychiatric illnesses. In patients with <u>mania</u>, both normal suppression (Schlesser et al 1980) and non-suppression (Shulman and Diewold 1977; Graham et al 1982) have been reported.

Schlesser et al (1980) reported normal suppression in schizophrenic patients, while others have demonstrated escape from normal suppression in patients with schizophrenia (Shulman and Diewold 1977; Dewan et al 1982; Meltzer et al 1982) and schizo-affective psychosis (Meltzer et al 1982). Coppen et al (1983), moreover, found escape from suppression in approximately one third of Type II schizophrenics, that is, with "negative" symptoms (flattening of affect, poverty of speech and loss of drive), but in only one tenth of those with Type I, with "positive" symptoms (delusions, hallucinations and thought disorder).

Several groups have reported abnormal results in alcoholic patients (Oxenkrug 1978; Fink et al 1981; Swartz and Dunner 1982; Coppen et al 1983), while few have found normal suppression (Brown et al 1979).

Workers have found abnormal DST results in 53% and 47% of patients with senile dementia without major depressive illness (Raskind et al 1982; Spar and Gerner 1982; Coppen et al 1983), in 44% of neurotics, other than those with neurotic depression (Coppen et al 1983) and in patients with anorexia nervosa who were below 80% of their ideal weight, regardless of their mood (Gerner and Gwirtsman 1981). Finally, Hällström et al (1983) found non-suppression in 15 out of 80 (19%) of normal women taking part in a population study; there were no differences between suppressors and non-suppressors as regards depressive symptoms and several other items.

The question may be raised: is the DST of any value in identifying a subgroup of depressives in people with epilepsy who are depressed? No studies have reported on this.

Chronic diphenylhydantoin (DPH) therapy causes alterations in cortisol metabolism (Werk et al 1964), as does that with phenobarbitone (PB) (Brooks et al 1972). Jubiz et al (1970) found abnormal results with the DST in patients on DPH therapy and postulated that a decrease in gastro-intestinal absorption, or an increase in the hepatic metabolism of dexamethasone, may account for the observation. Köbberling and zur Mühlen (1973) showed a marked decrease in dexamethasone suppressibility with both DPH and carbamazepine (CBZ) treated normal subjects. Mechanisms for the interference were postulated to be either that the drugs interfere with feedback mechanisms by decreasing the sensitivity to change in plasma glucocorticoid concentration, or that the drugs enhance the hepatic metabolism of dexamethasone. A criticism of this study is that the subjects had been treated with the anticonvulsants for one week, and it is possible that hepatic enzyme induction may not be evident after that short a time. The authors, however, favoured the CNS explanation. More recently Privitera

et al (1982) reported interference with the DST by CBZ in 9 psychiatric patients, 5 of whom had major endogenous bipolar depressive disorder. Although none had a diagnosis of epilepsy, 6 patients had abnormal electroencephalograms (EEGs). Carbamazepine treatment significantly elevated plasma cortisol values, regardless of the diagnosis or clinical state. As with other workers using the DST in patients on anticonvulsants, the authors felt that one explanation of the abnormality might be due to the induction of the hepatic microsomal enzyme system by CBZ. They mentioned another possibility: CBZ affects the neurotransmitters that regulate the release of corticotropin-releasing factor from the hypothalamus, and this may well have accounted for the abnormal results.

In conclusion, the area is one of rapidly growing research. The DST seems to be a useful method of confirming the diagnosis and monitoring the progress of primary major depressive illness, but it is not pathognomonic, as abnormal results have been reported in other conditions. The value of the test in identifying a subgroup of depressed patients with epilepsy has not been established.

CHAPTER 2

EPILEPSY

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2.1. History

Since antiquity, epilepsy has been recorded in the literature. In ancient Egypt it is found under the name "Labasu" (ca 2980 BC), in Biblical lands as "Seleniasmos", and in the Indian races, under the name "Apasara" (ca 600 BC) (Whitwell 1936). The first monograph on epilepsy appeared in the Hippocratic collection of medical writings about the year 400 BC, entitled "On the Sacred Disease". Hippocrates was far in advance of his times combating those who held epilepsy to be a supernatural or divine visitation. These he refuted with the statement that epilepsy, "the disease called 'sacred', is not, in my opinion, any more divine or more sacred than other diseases, but has a natural cause". He also referred in unmistakable terms to the aura of epilepsy, in his statement that "such as are habituated to their disease have a presentiment when an attack is imminent" (Bunker 1948).

Temkin (1971) traces the history of epilepsy through ancient medical science to medieval literature where it became known as the "falling sickness". Thereafter, the disease was thought to result from possession. Willis (1622-75) and contemporaries revolutionised the thinking about epilepsy with the notion that muscular motion is brought about by an explosion which involved chemical systems: "the animal spirits which lie in the middle of the brain will be affected and will explode. This would cause all the mental symptoms of the epileptic attack and a series of similar explosions occurring along the rest of the nervous system would bring about the convulsions of the body". Other names for the condition disappeared and it remained being called "epilepsy", which is the Greek name for a seizure (Temkin 1971).

Many of the myths about epilepsy were dispelled by John Hughlings Jackson in his work, "A Study of Convulsions" (1870), in which he outlined his views on unilateral epilepsy and attacks without loss of consciousness. Modern understanding of the condition was greatly enhanced with the advent of the EEG, the first recording being published by Hans Berger in 1929. Of this technique, Lennox has said that it had opened not merely a new chapter but a new volume in the study of epilepsy (Bunker 1948).

2.2. Definition and Classification of The Epilepsies

Epilepsy is defined as an occasional, excessive, disorderly discharge of nerve tissue, characterised by recurrent paroxysms leading to certain symptoms which are the result of excessive disordered cerebral activity (Marsden and Reynolds 1982). However, according to the authors, the word epilepsy is more than just the concept of a fit; a fit, a disease causing fits, a precipitating cause of fits, and the consequences of fits, all contribute to the overall picture of epilepsy.

Traditionally, epilepsy was divided into 3 main seizure groups - major or grand mal attacks, minor attacks including petit mal, myoclonic and akinetic seizures, and finally, psychomotor attacks characterised by psychic and motor phenomena, often associated with epileptogenic foci in the temporal lobes. In 1969, the International League Against Epilepsy published proposals for a new classification of epileptic seizures (Gastaut 1969a). Under this system seizures are divided into 2 main types - partial and generalised, depending on the origin and the extent of spread of the epileptic activity within the brain (Table 7). More recently, the Commission on Classification and Terminology of the International League Against Epilepsy (1981) proposed a revised clinical and EEG classification of epileptic seizures, but this has not been accepted by all as the definitive classification, most researchers adhering to the 1969 version.

Partial seizures are those of focal origin, which may remain focal or become generalised. Their symptomatology is described as elementary/simple or complex, the latter referring to an impairment of consciousness. In some there is impaired consciousness alone, while in others there may be a variety of symptoms such as dysmnesic disturbances (eg. "déjà vu"), ideational disturbances, illusions, hallucinations or automatisms.

Generalised seizures are due to bilateral and generally symmetrical disturbances and may take a variety of forms. Simple absences, which include the so-called "petit mal" attacks, consist of sudden, transient lapses of consciousness, accompanied by rhythmic 3 cycles per second (cps) spike and wave discharge on the EEG. Myoclonic seizures are also associated with momentary lapses of consciousness and, in addition, brief bilateral clonic jerking of muscle groups, the EEG usually showing polyspike and waves. The tonic-clonic seizure is the "grand mal" seizure and consists of bilateral tonic spasms and clonic jerks, with the EEG rhythm at 10 or more cps, decreasing in frequency and increasing in amplitude during the tonic phase, interrupted by slow waves during the clonic phase.

TABLE 7: CLASSIFICATION OF EPILEPTIC SEIZURES

(Adapted from the recommendations of the International League Against Epilepsy, 1969)

1. Partial Seizures or seizures beginning locally

(a) Simple or elementary (without impairment of consciousness)	i	With motor symptoms
	ii	With sensory symptoms
	iii	With autonomic symptoms
	iv	Compound forms
(b) Complex (with impairment of consciousness)	i	Impaired consciousness alone
	ii	With cognitive symptoms
	iii	With affective symptoms
	iv	With psychosensory symptoms
	v	With psychomotor symptoms
	vi	Compound forms

(c) Secondarily generalised

2. Generalised Seizures, bilateral symmetrical seizures or seizures without local onset

1. Absences	a)	Simple, with impairment of consciousness only ("petit mal")
	b)	Complex, associated with other phenomena

2. Myoclonus
3. Infantile spasms
4. Clonic seizures
5. Tonic seizures
6. Tonic-clonic seizures ("grand mal")
7. Atonic seizures
8. Akinetic seizures

3. Unilateral or predominantly unilateral seizures

4. Unclassified epileptic seizures

The term "status epilepticus" is used "when a seizure persists so long or is repeated so often as to constitute an established and persistent epileptic condition for hours or days" (Gastaut et al 1971).

Evoked epilepsies refer to the group of seizures which occur as a response to environmental stimuli, the commonest of which is light; it is estimated that at least 6% of recurrent seizures fall into this category of epilepsies (Ames 1982).

2.3. Epidemiology of Epilepsy

Estimates of the incidence and prevalence of epilepsy are probably an underestimation. In a sample of 17 general practices in London, only a fifth of patients with epilepsy had suspected the diagnosis before they decided to consult their doctors (Hopkins & Scambler 1977). Twenty to 25% of children in Newcastle suffering from seizures never sought medical advice (Miller et al 1960). Zieliński (1982) reviewed 36 studies investigating the prevalence of epilepsy and they varied from 1.3 per 1000 in Formosa to 19.5 per 1000 in Colombia; in over half the studies the rates lay between 4 and 10 per 1000. The generally quoted value is 5 per 1000 of the population (Hauser and Kurland 1975; Neugebauer and Susser 1979). More recently, Beran et al (1982) suggest that earlier prevalence reports are low, and propose a figure of 20 per 1000 or 2% of the population as a more realistic estimate. This means that at least from one in 50 to one in 200 people suffer from epilepsy. Studies show that there is probably some excess of the epilepsies among males (Neugebauer and Susser 1979; Zeiliński 1982).

2.4. Aetiology of Epilepsy

The aetiology of epilepsy is complex since it is a symptom of many disorders of the nervous system. Table 8 shows a classification of epileptogenic lesions.

TABLE 8: THE CLASSIFICATION OF EPILEPTOGENIC LESIONS

(Adapted from Mathieson 1982)

Lesions originating during intrauterine life

i) Disorders of cellular migration and differentiation
Hamartomas, tuberous sclerosis
ii) Disorders of vascular organisation
Arteriovenous malformations

Lesions associated with childbirth

i) Neonatal asphyxia
Cortical necrosis
ii) Excessive moulding
Medial temporal lobe lesions (incisural sclerosis)

Lesions resulting from febrile convulsions of childhood

Inflammatory lesions and their residua

Lesions resulting from head injury

Neoplasms

Metabolic encephalopathies

Hauser and Kurland (1975) in their epidemiological study found an underlying disease that could be considered a potential cause of epilepsy in 23.3% of cases. Ounsted et al (1966) demonstrated "organic insults" (gross acute or chronic intracranial disturbances) in 35% of their 100 children with TLE. There is, therefore, a significant proportion of cases where no cause can be established. This group of patients have been variously labelled "idiopathic", "cryptogenic" and "essential" epileptics, in contrast with the "symptomatic" and "organic" cases for whom the aetiology has been identified, of which the common causes have been listed. The proportion of patients presenting with "idiopathic epilepsy" is diminishing gradually as a consequence of increasing knowledge and improved techniques of neurological investigation.

2.4.i. Genetics

In his treatise on epilepsy, Hippocrates stated that "its origin, like that of other diseases, lies in heredity" (Livingston 1963). The genetics of epilepsy is complex, but there have been some convincing studies indicating an hereditary factor. Lennox (1951) in a large series of patients, reported an incidence of clinical epilepsy 7.2 times higher in relatives of patients with "essential" epilepsy and 3.6 times higher in relatives of patients with "symptomatic" epilepsy than in control groups. He also studied 122 twin pairs and found a concordance of 84% in monozygotic twins with respect to type of seizure and EEG pattern, the concordance for dizygotic twins being 10%.

Metrakos and Metrakos (1961; 1972) carried out investigations in families of epileptics with generalised seizures and proposed a dominant autosomal gene, of irregular penetrance, the expression of which varies with age, as it is weak at birth, and almost complete between the ages of 4 and 16, to decline afterwards. Metrakos and Metrakos (1972) also postulated an hereditary factor in febrile convulsions. Among 176 parents and 215 siblings of 88 probands who had febrile convulsions, the prevalence of convulsions was 17% for parents and 14.5% for siblings, approximately 5 times as high as that found for controls.

Several authors have reported an increased prevalence of EEG abnormalities in the relatives of patients with various forms of focal epilepsy. Bray and Wiser (1964) gave strong evidence for a genetic factor in TLE. Rodin and Gonzalez (1966) carried out EEGs on 80 families of epileptic patients and compared them to 30 normal control families. Abnormal EEGs were encountered in patients with both centrencephalic seizures as well as in patients with psychomotor epilepsy. One half of all patients with focal sharp waves or spike discharges were found to have another family member with an abnormal EEG. Patients whose seizures started between the ages of 6 and 15 years were thought to have a genetic component to their illness. Falconer (1971) reported that a positive family history of epilepsy, usually isolated convulsions in childhood, affecting parents or siblings, was found only in the groups with mesial temporal sclerosis or with scars and infarcts, occurring in 14% to 20% of cases, as against just under 1% of the general population. Gastaut (1969b)

implies a predilection to exhibit seizures once a lesion has been produced, rather than the transference of an epileptogenic structural abnormality. On the basis of his clinical practice observing the relatively high number of consanguineous marriages in parents of epileptics with generalised seizures, he postulates a recessive gene transmission.

In summary, although there seems to be an hereditary element in predisposing an individual to epilepsy, the exact mode of transmission is unknown, although after a review of the literature and tests of various modes of inheritance, it has been suggested (Gray 1982) that epilepsy is polygenically inherited.

In addition, several authors have noted a family history of psychiatric disorder in relatives of people with epilepsy. The Isle of Wight study (Rutter et al 1970) demonstrated that one fifth of the mothers of epileptic children had a nervous breakdown, whereas this was not observed in mothers of children with cerebral palsy. Taylor (1972) found that 37% of 100 patients with TLE who underwent surgery, had positive family histories of psychiatric disorders such as alcoholism, psychopathy or affective illnesses. Jensen and Larsen (1979a) reported that relatives of TLE patients have a high incidence of major psychiatric disorders compared with their frequency in the general population. Moreover, psychotic TLE patients had a much higher history of family psychopathology (65%) than did non-psychotic patients (39%). A study from Finland (Sillanpää 1973) showed high rates of divorce and illegitimacy among parents and guardians of epileptic children.

2.4.ii. Psychosocial Factors in People with Epilepsy

There is no doubt that social factors play a part in the life of a person with epilepsy. Burden (1981) cites 2 studies by medical anthropologists who reported some bizarre ideas which primitive people have about epilepsy. Both investigations revealed that the afflicted person had to live in a separate hut and be hidden away from strangers. They feared to touch someone in a seizure, believing that the evil spirits could leap over into someone near. Even in the western world today, stigma exists. Verduyn (1980) points out that, in common with non-epileptic patients, male sex, difficult temperament, early separation or loss experience, marital discord, parental psychiatric illness, large family size and overcrowding at home are associated with behaviour problems in the school child with epilepsy.

Bagley (1972), however, suggested that there are more of these adverse factors present in the environment of the child with epilepsy. Ounsted et al (1966) reported that 27% of their TLE sample came from seriously disordered homes. Bagley (1972) found a significant association between parents' adverse behaviour and attitudes and their epileptic child's disturbed behaviour.

Livingston (1963) points out that the most common of the behavioural difficulties in people with epilepsy are those related to anxiety or depressive states which stem, in most instances, from fear of being out of contact for a period of time, of injury or of death as a result of a seizure, or fear of having their disorder exposed to the general public. Caveness et al (1969) produced a survey of public attitudes in the USA towards epilepsy. There was an increased understanding of the condition from 1949 to 1969. Even in 1969, however, 4% of people familiar with the disorder still thought epilepsy was a form of insanity; 9% would object to their children playing with a child with epilepsy and 12% thought that epileptics ought not to be employed. Caveness and Gallup (1980) conducted another survey 10 years later and found that, in general, public attitudes towards people with epilepsy had improved further. The most favourable opinions were among the better educated, better employed, younger and urban members of the population. In Britain, in 1971, a similar survey revealed that only 57% of people felt that people with epilepsy should be employed, and 32% said that they would object to their child playing with a child with epilepsy (Betts 1982).

Bagley (1972) commented on the widespread social rejection of people with epilepsy and observed that this approach was to be found among professionals as well as the general public. Ryan et al (1980) prospectively investigated a sample of 445 individuals with epilepsy to assess the extent to which they felt stigmatised. The results showed that persons with epilepsy did not universally feel stigmatised by the disorder. However, a sociopsychological model of stigma was supported: the relationship between the severity of seizures and the perception of stigma due to the epilepsy was found to be highly dependent on other characteristics in the individual with epilepsy, such as the perception of employment discrimination, the perception of limitations imposed by the disorder, and the years of school attained by the person.

From the psychological point of view, it is well known that stress or anxiety can precipitate attacks in people with epilepsy (Livingston 1963; Betts 1981). On the other hand, pleasure, especially in childhood, may also precipitate a fit (Williams 1981).

Few authors have discussed epilepsy from the psychoanalytic point of view, the main ones being Kardiner, Clark and Stekel (Kardiner 1932). The basic thesis was that epilepsy represented "an excessive reaction formation against all previous traumas", and the seizure itself has, as its purpose, to repair the "damage done by the trauma" (Kardiner 1932).

2.4.iii. Biochemical Aspects of Epilepsy

Introduction

In epileptic attacks, an excessive synchronous discharge from a group of neurones can alter synaptic transmissions and affect various neurotransmitters. Neurotransmitters are particularly important in the initiation, spread and termination of seizures (Maynert et al 1975). GABA, ACh, 5HT, NA and DA are all neurotransmitters that have been studied in relation to the mechanisms of seizure activity or in relation to anticonvulsant drugs.

Good evidence from several lines of investigation suggests that brain amines play an important role in epilepsy. It is well known that pharmacologic agents that decrease endogenous brain amines increase susceptibility to experimental seizures, while agents that increase biogenic amines decrease the susceptibility to convulsions. For example, reserpine, a compound known to deplete brain amines, decreases the seizure threshold to pentylenetetrazol (Leptazol, Metrazol) (Lessin and Parks 1959), hyperbaric oxygen (Wada et al 1971), audiogenic stimuli (Boggan and Seiden 1971) and electroshock (Chen et al 1954; Azzaro et al 1972). Conversely, agents as some antidepressants that increase brain amines appear to protect animals from experimental seizures and protect some patients with generalised absence seizures (Fromm et al 1972). However, most of the TCAs which also increase brain amines tend to lower the seizure threshold (Trimble 1978b; Edwards 1979; Trimble 1980; Edwards and Glen-Bott 1983). Moreover, as discussed in the previous chapter, all the neurotransmitters and most substances implicated in seizures and epilepsy, were suggested as playing a part in the pathophysiology of depression.

Noradrenalin (NA)

An intraventricular injection of 6-Hydroxydopamine (6-OHDA), which causes a marked reduction of brain NA and DA levels, significantly lowered the electroconvulsive threshold in rats, and reduced the anticonvulsant activity of DPH, PB, and CBZ. Since no changes were found in rats whose noradrenergic neurones were protected against the neurotoxic action of 6-OHDA by desmethylimipramine, it was suggested that NA might be involved in the control of these phenomena (Crunelli et al 1981). That NA is involved in seizure susceptibility and CBZ activity, is also shown by the fact that clonidine, reported to decrease the firing rate of NA neurones in the brain, reduces the electroconvulsive threshold and the anticonvulsant effect of CBZ; further support comes from experiments showing that yohimbine, a substance known to block adrenergic sites activated by clonidine, has anticonvulsant activity of the same order as CBZ (Crunelli et al 1981). An anticonvulsant effect of yohimbine in mice has been reported (Chermat et al 1979). In addition, a number of animal experiments have demonstrated that the intraventricular injection of NA inhibited various kinds of induced seizures (Maynert et al 1975). Clonazepam, diazepam, DPH and PB all raise brain NA levels (Eadie and Tyrer 1980).

Dopamine (DA)

The dopaminergic effect on seizure susceptibility is not very clear. Dopamine, administered intraventricularly to mice, was shown to facilitate pentylenetetrazol seizures in low doses, and to antagonise such seizures in higher doses (Maynert et al 1975). Higher DA concentrations in the brain have been shown to increase irritability and motor activity (Maynert et al 1975). Infusion of Dopa into a carotid artery of an anaesthetised cat caused ipsilateral EEG activation (Dagirmanjian et al 1963). Hughes, quoted by McPherson (1970) reported a significantly lower incidence of epileptic seizures in patients with Parkinson's disease than the general population. It had also been noted that the Parkinsonian patients appeared to have supranormal resistance to convulsant drugs such as pentylenetetrazol. McPherson (1970) reported 3 patients with Parkinson's disease who developed seizures and EEG changes when treated with levodopa, although the vast majority of patients showed no such EEG changes. Drugs that affect the DA system like reserpine, thioridazine and chlorpromazine are shown to increase seizure susceptibility (Vaughan et al 1955; Stewart 1957; Hollister and Barthel 1959; Boggen and Seiden 1971).

Several studies have investigated CSF HVA. Ito et al (1980) reported significantly increased HVA in CSF of children with infantile spasms. Papeschi et al (1972) found very low values of HVA in 4 patients with TLE, even lower than that in patients with Parkinson's disease.

The importance of the dopaminergic system in relation to anticonvulsant drugs is still uncertain. Some workers (Chadwick et al 1976; Elliot et al 1977) reported the extrapyramidal syndrome in some patients receiving high doses of DPH is due to the dopaminergic blocking action of the drug. Chadwick et al (1977) reported a slight rise in HVA in treated epileptic patients. Laxer et al (1979) found low concentrations of HVA in lumbar CSF when compared to controls, but only in untreated patients, the treated patients having values in the normal range.

There seems to be some agreement that the dopaminergic system is involved in reflex epilepsy. Apomorphine, a DA agonist, was proposed as a treatment for epilepsy by British and French neurologists in the nineteenth century (Anlezark et al 1981). More recently, the cessation of experimentally produced audiogenic seizures in mice, and photosensitive epilepsy in baboons, by DA agonists has been described (Meldrum et al 1975a; Quesney 1980; Anlezark et al 1981), suggesting that DA plays a role in protection against reflex epilepsy. Conversely, the protective effects of apomorphine in animal models can be antagonised by appropriate doses of phenothiazines, butyrophenones or other DA antagonists (Meldrum et al 1975a; Quesney 1980).

A definite protective effect of low doses of apomorphine has been observed in patients with primary cortical generalised photosensitive epilepsy (Quesney et al 1980). Lhermitte et al (1972) described a powerful therapeutic effect of chronic L Dopa, or of L Dopa acutely plus an inhibitor of peripheral dopa-decarboxylase in a case of post-anoxic reflex myoclonus. Subsequently, L Dopa and apomorphine were reported to slightly improve the neurological status of 2 patients with myoclonus (Van Woert and Sethy 1975). Apomorphine blocks epileptic photosensitivity in some patients with primary and secondary generalised epilepsy (Andermann et al 1977).

In conclusion, it seems that DA agonists can inhibit photosensitive generalised epilepsy and photomyoclonic responses both experimentally and clinically.

5 Hydroxytryptamine (5HT; serotonin)

Depletion of central 5HT stores is associated with a lower convulsive threshold and an increase in serotonergic transmission increases the convulsive threshold (Chase et al 1969), especially in photically induced epilepsy (Meldrum et al 1975b). Depletion of brain 5HT has been associated with a fall in seizure threshold in mice and the photosensitive baboon, Papio Papio (Chen et al 1954; Wada et al 1972).

Evidence has been accumulating that certain types of intention myoclonus may be associated with a deficiency of 5HT in the CNS. Several studies reported low CSF 5HIAA in patients with myoclonus (Chadwick et al 1975b; Van Woert and Sethy 1975; Van Woert et al 1977; Van Woert and Rosenbaum 1979). Clinical investigations have indicated that precursors of 5HT have antimyoclonic action. Myoclonic movements have been successfully treated with 1) high doses of L-5-hydroxytryptophan (L-5HTP), the immediate precursor of 5HT, in combination with the peripheral decarboxylase inhibitor, carbidopa (Chadwick et al 1975b; Van Woert and Sethy 1975; Van Woert and Rosenbaum 1979), and 2) low doses of L-5HTP plus carbidopa, in conjunction with the specific 5HT uptake inhibitor fluoxetine (Van Woert et al 1980). In addition, methysergide, which inhibits serotonergic neurotransmission by blocking the 5HT receptor site, has been observed to counteract the antimyoclonic action of L-5HTP with carbidopa in a patient with post-anoxic intention myoclonus (Magnussen et al 1978).

Myoclonus has been successfully treated with clonazepam (Chadwick et al 1975b) which has been shown to cause a rise in brain 5HT and 5HIAA in mice (Jenner et al 1975), and which leads to an increase of CSF 5HIAA in patients after treatment (Chadwick et al 1975b). In addition, the insecticide p,p'-DDT produces stimulus - sensitive intention myoclonus in humans and rodents (Garcin et al 1965; Chung Hwang and Van Woert 1978). The DDT-induced myoclonus in rodents has been found to be reduced by drugs which enhance brain serotonergic mechanisms and aggravated by 5HT antagonists (Chung Hwang and Van Woert 1978). Lhermitte et al (1972) described a patient with post anoxic myoclonus who was successfully treated with 5HTP.

In contrast, experimental myoclonus has been produced in immature guinea pigs and rats by intraperitoneal injection of L-5HTP (Klawans et al 1973; Stewart et al 1976). When the brain serotonergic receptors are supersensitised by intracisternal injection of 5, 7 dihydroxytryptamine, myoclonus can be induced by even lower doses of L-5HTP (Stewart et al 1976). This suggests that a type of myoclonus can be produced by

stimulating brain 5HT receptors in some species. Growdon (1977) provided interesting and seemingly conflicting findings: he demonstrated that from 5 to 60 minutes after an injection of p-chloroamphetamine, a drug which releases 5HT into brain synapses, a myoclonic syndrome can be produced in rats. He found, however, normal levels of whole brain 5HT and 5HIAA at the time of the syndrome, but significantly reduced levels on the following day. Bonnycastle et al (1957) reported elevated brain 5HT in anticonvulsant treated rodents.

Several authors have studied the concentrations of 5HIAA in the lumbar CSF of epileptic patients both on and off anticonvulsant treatment, but their results have not been consistent.

Normal CSF 5HIAA levels have been found in children with infantile spasms, when compared to controls (Ito et al 1980). Decreased levels of 5HIAA in the CSF of epileptics were found when compared to controls, although the figures did not reach statistical significance (Laxer et al 1979). Two studies have examined ventricular CSF content of 5HIAA from patients with epilepsy, one finding reduced levels (Papeschi et al 1972), while the other found normal values (Bossi et al 1981).

Significantly reduced 5HIAA levels were found in 3 untreated and 11 anticonvulsant treated epileptic children (Shaywitz et al 1975), and in 2 untreated and 10 treated patients with temporal lobe and tonic-clonic seizures (Garelis and Sourkes 1974). Young et al (1980) found normal lumbar CSF 5HIAA in untreated patients, but a significant lowering of the 5HIAA was found in anticonvulsant treated patients, from which the authors concluded the low levels were due to the decreased rate of 5HT metabolism induced by the anticonvulsant drugs. Lhermitte et al (1972) also described low CSF 5HIAA in a patient treated with PB. Chadwick et al (1975a) found significantly raised CSF 5HIAA in 27 treated epileptics, compared with 15 untreated epileptics, and 22 neurological controls: the rise was only seen when therapeutic blood levels had been achieved and was most striking in clinically intoxicated patients. Chadwick et al (1977) found an elevation in CSF tryptophan and a trend towards elevation of 5HIAA in 46 treated epileptics, but normal concentrations in a smaller group of 26 untreated patients: the authors commented that the rise in the 2 substances appeared related to the number of anticonvulsants administered, and the serum levels of PB and DPH. Clonazepam, PB and DPH all raise brain 5HT levels (Eadie and Tyrer 1980). Anticonvulsant drugs in high doses increase the cerebral content of 5HT in rodents (Jenner et al 1975). Valproate produces an increase in 5HIAA concentration (Horton et al 1977).

It does not seem clear in man whether anticonvulsant drugs increase or decrease the turnover of 5HT. It seems doubtful that any such changes in 5HT metabolism contribute directly to the therapeutic action of anticonvulsant drugs, but the finding that maximal elevation of CSF 5HIAA is seen in anticonvulsant treated patients may indicate an involvement for 5HT in the acute neurotoxic effects of anticonvulsant drugs (Chadwick et al 1977).

Conflicting results possibly reflect differences in the patient samples with regard to type and duration of both epilepsy and treatment, and also in the procedure in the taking of and analysis of the CSF.

In conclusion, it seems probable that 5HT is involved in the pathophysiology of epilepsy and mode of action of anticonvulsant medication, but apart from the low serotonergic activity in intention myoclonus, the precise mechanisms involved are at present uncertain.

Gamma-aminobutyric acid (GABA)

Several recent studies have indicated the importance of GABA in the neurochemistry of epilepsy (Maynert et al 1975; Wood 1975). GABA-ergic neurones are essentially inhibitory neurones and appear to be important in prevention, spread or build up of seizures (Meldrum 1975). Experimental impairment of GABA functioning has been shown to reduce the convulsive threshold (Wood 1975), and reduction in brain GABA concentration by 40% leads to generalised tonic-clonic seizures (Maynert et al 1975). In addition, compounds such as picrotoxin and bicuculline, which block GABA at its receptors, are convulsants (Maynert et al 1975). Other evidence for suggesting that a reduction of this inhibitory substance could be responsible for seizure activity comes from biochemical studies which have shown decreases of GABA (van Gelder et al 1972), its synthesising enzyme glutamic acid decarboxylase (GAD) (Emson and Joseph 1975; Wood 1975) and GAD-containing axon terminals (Ribak et al 1981), at seizure foci. In addition, low mean CSF GABA levels have been reported in children with febrile convulsions and epilepsy (Löscher et al 1981; Schmidt and Löscher 1981) and in patients with epilepsy, especially those with tonic-clonic generalised and complex partial seizures (Wood et al 1979; Manyam et al 1980). Since CSF GABA is thought to reflect brain GABA concentrations, these reports suggest further an impaired GABA metabolism in brain of seizure patients, but it may only be a secondary phenomenon due to the convulsion (Löscher et al 1981).

Oral administration of GABA has been reported to inhibit generalised tonic-clonic convulsions or generalised absence seizures (Tower 1961). GABA, however, is shown to poorly penetrate the blood brain barrier (Kuriyama and Sze 1971) and is not clinically valuable as an anticonvulsant. Phenytoin has been reported to increase the frequency of discharge of GABAergic neurones (Julien and Halpern 1972). Phenobarbitone is thought to enhance GABA-mediated post-synaptic inhibition as part of its anti-convulsant activity both experimentally and in patients (MacDonald and Barker 1977; Meldrum 1982b). Ethosuximide raises brain GABA levels in experimental animals (Eadie and Tyrer 1980). The benzodiazepines produce enhancement of GABAergic inhibition (Costa and Guidotti 1979; Meldrum 1982b), while VPA is shown to induce GABA accumulation in the brain after intraperitoneal injection (Godin et al 1969; Horton et al 1977). A relationship between an increase in cerebral GABA concentration and protection from audiogenic seizures has been described (Simler et al 1973).

Horton et al (1977) made the point that the exact mechanism and significance of the increase in brain GABA concentration following VPA is uncertain. Perry and Hansen (1978) have shown that oral doses of VPA do not increase the GABA concentration in the rat brain. Nevertheless enhancement of GABA mediated inhibition can be considered as a possible mechanism of VPA action in animals. It is clearly established that VPA in vitro has inhibitory actions on three enzymes concerned with GABA metabolism, and when high doses of VPA are given acutely to animals, they produce an increase in brain GABA content: the increase is small, but it has been demonstrated to occur largely in synaptosomal fractions (Meldrum 1980).

The exact basis for the antiepileptic action of low and chronic doses of VPA in man is not clear. That VPA is anticonvulsant is established (Jeavons et al 1977; Bruni and Wilder 1979; van der Zwan 1980), and indeed, it has been suggested that its antiepileptic activity is related to its ability to raise GABA levels (Bruni and Wilder 1979; Turner and Whittle 1980; Meldrum 1982b). It is of interest that recently there has been some evidence for GABA-5HT interaction in certain serotonergic neurones (Pujol et al 1981).

In conclusion, there is good evidence to support the notion that a reduction of GABA may result in a lowering of the seizure threshold or cause convulsions. In addition, many of the recognised anticonvulsants, at least as part of their anticonvulsant activity, are thought in one way or another, to facilitate GABA-ergic inhibition.

Acetylcholine (ACh)

The possible involvement of cholinergic pathways in epileptic seizures was indicated by Tower and McEarchern (1949), who reviewed the literature and found 3 European case reports of ACh in the CSF of patients with epilepsy. They also reviewed about a dozen studies reporting an increase in cortical activity on the EEG with local application of ACh. This led them to conduct a study which showed that the CSF of 44 (77%) epileptics contained ACh, compared with its presence in only 8 (5%) of control subjects. They suggested, moreover, that the presence of ACh in the CSF of epileptics was related to the occurrence and frequency of seizures, and the extent of their EEG abnormalities. Later, it was reported that cortical epileptogenic foci contain high stores of ACh (Tower 1960). However, further studies in this area did not seem to support the initial findings by Tower. However, it has been suggested that epileptic foci contain increased levels of acetylcholinesterase (Maynert et al 1975). Apart from poisoning with anticholinesterases, no epileptic syndrome in man has been shown to be related to either impaired or augmented central cholinergic function (Meldrum 1978). Several workers demonstrated that certain anticonvulsant drugs increased the ACh concentration in certain areas of the brain: both schools felt that the anticonvulsants influenced the ACh indirectly (Bianchi et al 1975; Consolo et al 1976).

The hypothalamic-pituitary axis

A recent investigation (Dana-Haeri 1982) evaluated the hypothalamic-pituitary axis in patients with epilepsy on anticonvulsant medication. Results showed that serum LH and sex hormone binding globulin (SHBG) were elevated in both male and female patients, while the free testosterone fraction was significantly lowered in male epileptic patients when compared to a control group of normal volunteers. Baseline PRL levels remained within the normal range. Results broadly agree with those of Toone et al (1980) who reported significantly elevated levels of LH and SHBG, but significantly elevated total plasma testosterone and PRL levels in a group of male patients on combinations of antiepileptic drugs, when compared with normal controls.

The effect of seizure activity on hypothalamic-pituitary function was also determined (Dana-Haeri 1982): the PRL and LH were significantly increased 20 minutes after generalised tonic-clonic attacks, while PRL levels dropped to near baseline levels 60 minutes after the attack, LH levels remaining significantly elevated. The PRL also rose 20 minutes

after complex partial seizures, but not with simple partial attacks, the latter, by definition, having no alterations of consciousness. These results confirm the findings of others (Trimble 1978a; Abbott et al 1980; Collins et al 1982; Höppener et al 1982), who found PRL elevation 15 to 20 minutes after major generalised tonic-clonic seizures and ECT, but not with hysterical attacks. Höppener et al (1982) also reported elevated PRL levels in 80% of patients with complex partial seizures.

The role of the biogenic amines and prolactin should be mentioned. Prolactin release from the anterior pituitary gland is thought to be controlled by the release of neurotransmitters by the hypothalamus. Inhibition by DA (Kamberi et al 1971; Schaar and Clemens 1974; Herbert 1982) is widely recognised and important, but NA (Schaar and Clemens 1974) and GABA (Schally et al 1977) may also inhibit PRL release. The effect of 5HT on PRL release in man is unclear (Abbott et al 1980), although Kato et al (1974) suggest that a serotonergic mechanism is involved.

An anticonvulsant action of ACTH was first reported by Klein and Livingston (1950), who observed a temporary beneficial response in 4 out of 6 epileptic children. Subsequently, the anticonvulsant efficacy of ACTH was confirmed in larger groups of patients with hypsarrythmia and infantile spasms (Stamps et al 1959; Millichap and Bickford 1962) and in children with generalised absence seizures (Miribel and Poirier 1961), but the mechanism of its action was undetermined. On the other hand, Hoefer and Glazer (1950), cited by Klein and Livingston (1950), showed that after treatment with ACTH, abnormal EEGs appeared in patients who had normal tracings before treatment. In animal studies, Woodbury (1952) reported that ACTH raised the threshold to electroshock in rats by 11% after 28 days. These results are in contrast to those of Wasserman et al (1965) who reported a significantly lowered shock threshold in rats which was correlated with an increase in the concentration of intracellular sodium in the brain.

Folic acid (FA) and epilepsy

A relationship between FA, epilepsy and anticonvulsant drugs was first implied by Mannheimer et al (1952). Soon after Badenoch (1954) and Hawkins and Meynell (1958) described 2 and 8 epileptic patients respectively, with megaloblastic macrocytic anaemia caused by anticonvulsant drugs, one of whom had a good response to vitamin B12 alone while the others responded to FA. The latter authors reported a remarkable improvement in fit frequency in 6 out of 8 patients after treatment of the anaemia. Chanarin et al (1960),

however, described an epileptic patient with megaloblastic anaemia due to PB who, on 2 occasions, reacted with an increase in the number of seizures after intramuscular injections of FA. The authors suggested that the FA had a convulsant action in the patient. The same conclusion was made by some (Reynolds 1967; Wells 1968; Lanzkowsky et al 1969; Neubauer 1970), but refuted by many others (Hawkins and Maynell 1958; Jensen and Olesen 1970; Ralston et al 1970; Houben et al 1971; Norris and Pratt 1971; Mattson et al 1973). It is perhaps conceivable that there exists a subgroup of epileptic patients who are indeed sensitive to higher FA levels, as several reports suggest (Chanarin et al 1960; Chien et al 1975; Rodin 1982). What seems clear, however, is that an increase of serum FA levels decreases serum DPH and/or PB levels (Jensen and Olesen 1970; Baylis et al 1971; Mattson et al 1973). In this context it is interesting that FA itself and its derivatives have convulsant properties in animals (Noell et al 1960; Hommes and Obbens 1972), and the FA content of experimental foci is increased (Mayersdorf et al 1971).

The megaloblastic anaemia is reported to be comparatively rare and occurs in less than 1% of treated epileptics (Hawkins and Maynell 1958; Reynolds et al 1966a). The incidence of macrocytosis in anticonvulsant treated epileptics is 11% to 53% (Hawkins and Maynell 1958; Klipstein 1964; Reynolds et al 1966a; Malpas et al 1966; Ibbotson et al 1967), and megaloblastic haemopoiesis 38% (Reynolds et al 1966a). Reynolds et al (1966b) reported 2 epileptic patients who had prolonged retarded depression. They pointed out that it was likely that the patients had drug induced FA deficiency for many years before they became anaemic: also, the patients gave a history of psychiatric illness before they presented with anaemia, but some years after commencing anticonvulsant therapy.

There are many reports of abnormally low serum FA levels from 27% to 91% of patients treated with anticonvulsant drugs (Druskin et al 1962; Malpas et al 1966; Wells and Casey 1967; Norris and Pratt 1971; Preece et al 1971; Houben et al 1971; Reynolds et al 1966a; 1971b; Jensen and Olesen 1969; 1970; Reynolds 1975). Reynolds (1975) reviewed the literature and included 10 studies not mentioned in this text, where subnormal serum FA values were found in drug treated epileptic patients. Low levels were commonly associated with multiple drug therapy, especially including DPH, but PB and PR were also incriminated. Several investigators have reported an associated fall in CSF FA concentration (Wells and Casey 1967; Reynolds et al 1969; 1971a; Reynolds 1975), although this was not found by others (Weckman and Lehtovaara 1969).

Moreover, there are several studies in which epileptics with psychiatric illness are reported to have significantly more reduced serum FA levels (Callaghan et al 1969; Bruens 1971; Reynolds et al 1971b), especially implicating depressed epileptics (Snaith et al 1970; Trimble et al 1980; Rodin 1982).

Trimble et al (1980) reviewed 19 studies of both epileptic and non-epileptic patients, with psychiatric disturbances, which indicated a relationship of the latter to abnormalities of FA. The studies indicated the following. First, a relationship exists between the receiving of anticonvulsant drugs, in particular DPH, and a low serum FA. Second, in adults with epilepsy who have psychiatric disturbances the red cell FA and serum FA were abnormally low. Mean serum levels for the affected patients ranged from 1.8µg/l to 4.14µg/l, and although no specific diagnosis was implicated, it generally seemed that the patients who were more severely psychiatrically disturbed, particularly the psychotic and demented, were those with the lowest mean values. Further, abnormally low levels were noted in both in-patient and out-patient studies (Reynolds et al 1971b) suggesting that the association is not solely due to hospitalisation.

In conclusion, it is well described in the literature that FA metabolism and anticonvulsant medication may be related. Reynolds (1976) states that the cause of the FA deficiency is primarily the anticonvulsant therapy, with DPH, PB and PR being the drugs particularly implicated, but Reynolds et al (1966a) found no clear relationship between FA concentration and duration of drug therapy. Several hypotheses have been forwarded to explain a presumed defect of FA metabolism, including interference with FA coenzyme formation and function (Baker et al 1962; Hawkins and Meynell 1958), a competitive effect (Girdwood and Lenman 1956), displacement of FA from its carrier protein (Klipstein 1964), and a mild stress on the FA through the increased parahydroxylation process during the metabolism of the anticonvulsant drugs (Kutt et al 1964). Increased utilisation of FA may play a role: Gatenby (1960) reported that megaloblastic anaemia is more likely to develop when anticonvulsants are used in pregnancy.

Moreover, that there is a relationship between FA, monoamines and epilepsy has also been suggested (Chadwick et al 1975a; Reynolds et al 1975).

2.5. Treatment of Epilepsy

Today, treatment is directed initially towards any possible cause, and next it aims at controlling the primary symptoms, namely the epileptic seizures. Pharmacological agents have become the standard form of treatment and the most widely used anticonvulsants, their trade names and year of introduction are presented in Table 9.

Experience has shown that some seizure types respond better to certain anticonvulsant drugs than others. Generalised absence seizures were until recently best controlled by ethosuximide and troxidone. Sodium valproate has now become the drug of choice for such attacks, which include absences, typical or atypical, myoclonic epilepsies and some photosensitive epilepsies (Jeavons and Clark 1974; Simon and Penry 1975; Jeavons et al 1977). Phenobarbitone, PR, of which the major metabolite is PB, and DPH have proved useful in the treatment of major generalised (tonic-clonic) and partial seizures, but are not recommended for the treatment of minor seizures (Eadie and Tyrer 1980). Most reports indicate that CBZ is effective in the treatment of major generalised and partial seizures, particularly those with complex symptomatology or psychomotor seizures (Bird et al 1966; Rodin et al 1974; Troupin et al 1977).

Sulthiame can be a useful medication in some patients with TLE with partial seizures, but there is an increasing impression that it is not a very effective antiepileptic drug (Eadie and Tyrer 1980). Chlormethiazole (Heminevrin) can be used intravenously as an anticonvulsant for status epilepticus, but it has too great a dependence potential and is too rapidly eliminated to be suitable for use orally in maintenance therapy (Eadie and Tyrer 1980). Acetazolamide (Diamox) has been used with success in children: it has been shown that seizure control could be improved and maintained for between 2 and 5 years, when patients with CBZ-resistant generalised tonic-clonic and temporal lobe seizures were given acetazolamide as adjunctive therapy (Forsythe et al 1981).

The benzodiazepines, diazepam and lorazepam, have proved useful given intravenously (Gastaut et al 1965; Waltregny and Dargent 1975), and diazepam per rectum either as a suppository or solution (Agurell et al 1975; Munthe-Kaas 1980), in the treatment of status epilepticus, but they are generally not used orally for chronic control as the doses needed to achieve anticonvulsant effects are large and give rise to unwanted side effects. Clonazepam is useful intravenously in status

TABLE 9: THE MAJOR ANTICONVULSANT DRUGS

(Compiled from Eadie and Tyrer 1980, except where otherwise indicated)

Generic Name	Trade Name	Year Of Introduction	Therapeutic Range (μmol/L)	Half Life (hours) Adults	Hepatic Enzyme Induction
Phenobarbitone (Phenobarbital)	Luminal Gardenal	1912	45 - 130	70 - 100	Yes[1]
Phenytoin (Diphenylhydantoin)	Dilantin Epanutin	1938	40 - 80	15 - 20	Yes[1]
Troxidone	Tridione Paradione Trimethadione[6]	1945	> 5000	16	No[3]
Ethosuximide	Zarontin	1951	300 - 700	30 - 70	No[5]
Primidone (Major Metabolite Phenobarbitone)	Mysoline	1952	45 - 130	6 - 12	Yes[1]
Acetazolamide[7]	Diamox[7]	1954[7]	250 - 1000[7]	8[8]	Unknown[7]
Carbamazepine	Tegretol	1961	25 - 50	25 - 50	Yes[1]
Sulthiame	Ospolot	1963	-	-	-
Clonazepam	Rivotril Clonopin[4]	1970	0.08 - 0.24	24 - 36	Uncertain[1]
Valproic Acid (Sodium Valproate)	Epilim Depakene[4]	1973	300 - 600	8 - 10	No[2]

References:

1) Richens 1976
2) Oxley et al 1979; Perucca and Richens 1979
3) Conney 1967
4) Editorial 1977
5) Gilbert et al 1974
6) Sapieka 1966
7) Personal Communication - Lederle Laboratories
8) Bennett et al 1974

epilepticus (Gastaut et al 1971) and is said to be useful orally in the amelioration of the majority of seizure types with only transient side effects (Fazio et al 1975). Other authors (Dreifuss et al 1975; Browne and Feldman 1980) comment on its usefulness as a single drug in absence seizures, or as adjunctive therapy for other seizure types, but both report on the occurrance of frequent drowsiness, ataxia and hyperactivity (in children), quite often necessitating discontinuation of the drug. More recently, a 1,5 benzodiazepine, clobazam has been shown to be anticonvulsant given orally in both open (Gastaut and Low 1979) and controlled (Critchley et al 1981; Allen et al 1983) trials, as adjunctive therapy in poorly controlled epilepsy, especially complex partial seizures.

Rodin (1972) reviewed the success of medical treatment of epilepsy and concluded that a 2 year terminal remission rate, that is free of seizures, occurs in about 30% of patients: the 5 year figure is around 17% while the 10 year figure is approximately 10%. He made the point that the often quoted figure of 60% to 80% of all patients being controlled with modern anticonvulsants is a myth resulting from a loose definition of the term "control", and inadequate follow-up or both.

If epilepsy is partly but not fully controlled, anticonvulsant therapy should be continued indefinitely. Full control of epilepsy means that the patient shows no clinical or EEG evidence of any epileptic manifestation, however minor: full control does not mean merely that the patient is free from severe seizures. After epilepsy has been fully controlled, many believe that anticonvulsants should be continued in full dosage for between 2 and 4 years before a withdrawal of treatment is contemplated (Eadie and Tyrer 1980).

A major advance in the treatment of epilepsy has been serum anticonvulsant monitoring. Evidence has suggested that anticonvulsant and toxic side effects of many drugs are more closely related to the level of the drug in the serum rather than to the dosage. Patients kept on a specified drug dose may have varying serum anticonvulsant levels. Factors affecting these levels can be patient factors or drug factors. The patient factors include age, sex, genetic differences, weight, pregnancy, liver function or disease, renal function or disease, food intake, time of sampling, malabsorption and poor compliance. Drug factors include pharmaceutical quality, drug interactions, which are especially important if the individual is on more than one anticonvulsant or certain other groups of drugs, and bioavailability. Clinically, serum anticonvulsant monitoring is widely used (Gibberd et al 1970; Eadie and Tyrer 1980).

From research in the area, the concept of the "therapeutic range" has emerged. The "therapeutic" or "optimal" range of plasma drug concentrations should be that range of plasma drug levels associated with the best chance of obtaining the desired therapeutic effect in the majority of patients, but with minimal neurotoxic side effects. With regards to the anticonvulsants, plasma drug levels below the therapeutic range are likely to be associated with an inadequate response to treatment. Idiosyncratic reactions, which by their nature are rare, may be associated with any plasma drug level. Commonly quoted therapeutic ranges of the main anticonvulsant drugs are shown in Table 9. The upper limit of the range is arrived at from studies which document the serum levels at which side effects such as ataxia, nystagmus, diplopia, drowsiness and confusion occur. Eadie and Tyrer (1980) point out that the therapeutic ranges for many drugs quoted in the literature have usually been defined without rigorous statistical analysis, but in practice the ranges prove useful as a guide to therapy. Drug intoxication may, however, be present in the absence of the classical clinical signs, and with subtherapeutic blood levels, particularly in children and mentally retarded patients (Kaufman and Katz-Garris 1979; Weiss et al 1969), and can cause depression, psychosis, aggravation of behaviour disorders, dementia, confusion, and stupor (Trimble and Reynolds 1976).

The serum concentrations of the anticonvulsant measured represents both bound and free or unbound fractions. It is generally assumed that the pharmacological properties of a drug arise from the free or diffusable rather than the bound portion. Free anticonvulsant levels are believed to be better correlated with the clinical response and degree of intoxication than the total serum concentrations, especially if a large proportion of the drug is protein bound as in the case of DPH, VPA and CBZ (Booker and Darcey 1973; Levy 1982a). Traditionally the serum anticonvulsant levels are measured; the value of this rests on the assumption of a close correlation between drug levels in the plasma and in the brain and depends on a constant degree of plasma protein binding between individuals. In some instances the anticonvulsant drug protein binding is disturbed, as in infancy, pregnancy, renal failure, hypoalbuminaemia, or because of competition by other drugs. In such circumstances it is suggested that valid monitoring can be expected only from the measurement of the free or unbound fraction of those drugs. Levy (1982a) proposed new techniques for reliable measurement of the free serum fraction of DPH and CBZ. As salivary DPH concentrations correlate closely with plasma free drug concentrations, this method of monitoring

may be more appropriate at certain times in adults, and always in children (Reynolds et al 1976; Knott et al 1982).

Absorption and elimination of a drug are assumed to follow exponential kinetics; that is, a constant fraction of the drug present is eliminated per unit of time. The rate of the exponential process may be expressed in several ways, or by its half-life, the time required for 50% completion of the process (Fingl and Woodbury 1975). If a drug is given at a constant dosage and at fixed intervals shorter than the elimination time of the drug, the drug concentration in plasma will rise in a series of steps. The steady state of a drug is reached at which the amount of drug absorption equals the amount of drug elimination over each dosage interval. The longer the half-life, the smaller is the dosage or the longer is the dosage interval necessary for a drug to achieve a particular steady state concentration (Eadie and Tyrer 1980). The half-lives of the common anticonvulsants are shown in Table 9.

The hepatic microsomal drug metabolising systems are enzyme systems located in the liver endoplasmic reticulum and are not only concerned with the biotransformation of many drugs, but, in addition, their activity can be induced by many drugs (Fingl and Woodbury 1975), including most of the anticonvulsants (See Table 9). This has important clinical and therapeutic implications. Consequences of hepatical microsomal induction include an increased turnover of endogenous substances, a tentative explanation for the FA deficiency in many drug treated epileptics, especially those with psychiatric complications, and an increased turnover of drugs, including other anticonvulsants, steroid compounds and some of the TCAs (Richens 1976).

As there are many psychosocial concomitants of a diagnosis of epilepsy, in addition to medication, other avenues of treatment should not be forgotten. Ames (1982) makes the point that recognition and consequent avoidance of factors, such as flickering lights on television screens, which lead to the "evoked epilepsies" is an important factor in the management of these epilepsies. Supportive psychotherapy is valuable in helping a person to come to terms with the fact that he or she has epilepsy (Betts 1981). The behaviour problems of a person with epilepsy may be amenable to behaviour modification techniques (Henriksen 1977), and indeed, behaviour therapy has been found useful in seizure control (Mostofsky 1977; Lavender 1981). Several studies have suggested that EEG feedback training may be of variable benefit in controlling medically refractory epilepsy (Kaplan 1975; Wyler et al 1979) but the precise

mechanism for the beneficial effect it has is unclear. Long-term casework support by a psychiatric social worker can help both the patients who have fits more frequently at times of social stress, by arranging regular discussions and additional crisis interviews, and also the group of patients whose fits are well controlled but whose personality problems remain unsolved (Tavriger 1977).

Ward and Bower (1978) and Tavriger (1966) describe parental anxieties and fantasies about their children with epilepsy, which probably constitute management problems.

Finally, patients with intractable seizures may need their temporal lobes resected (Penfield and Flanigin 1950; Falconer 1973). Ward (1983) states the criteria for patient selection for surgical treatment of epilepsy are relatively standardised and involve 3 essential elements: the first is that the seizures must be refractory to therapy with anticonvulsant drugs; the second, that the seizures must be of a focal origin; finally, the focus must be in "dispensable cortex" ie. cortex which can be resected without an unacceptable neurological deficit.

2.6. Psychiatric Aspects of Epilepsy

That there is a relationship between epilepsy and psychiatric illness has been suggested for some time. There are broadly 2 groups of psychiatric disorders found in people with epilepsy. Firstly, the peri-ictal syndromes, being those directly connected with clinical epileptic attacks, and secondly the inter-ictal states. The ictal symptoms include complex auras, during which the patient may experience hallucinations; pre-ictal states during which the patient becomes increasingly irritable; and post-ictal states with confusion, paranoid ideation and hallucinations (Pond 1957).

There are several types of inter-ictal psychiatric disturbances. Rutter et al (1970) demonstrated that this is not simply due to having a chronic illness: they examined children aged between 5 and 14 years and found that the group with epilepsy had not only considerably more psychiatric disturbance than healthy children, but also 3 times as much disability than those with other chronic illnesses, affecting the peripheral rather than the central nervous system. The history of the relationship between psychiatric disturbances and epilepsy has been summarised by Guerrant et al (1962) and is shown in Table 10.

TABLE 10: HISTORY OF PERSONALITY CHANGES IN PEOPLE WITH EPILEPSY

(From Guerrant et al 1962)

Period	Proponents	Dates
Period of Epileptic Deterioration	Gowers, Letchworth	(- 1900)
Period of the Epileptic Character	Morel, Turner, Clark	(1900 - 1930)
Period of Normality	Dana, Lennox	(1930 -)
Period of Psychomotor Peculiarity	Gibbs	(1948 -)

Early writers, such as Gowers, suggested that the personality changes of patients with epilepsy were consequent to their fits. Letchworth wrote that the "permanent decrease in intellectual and moral tone is expressed in the term Epileptic Deterioration". Later writers such as Turner felt, unlike Gowers, that the epilepsy and the psychiatric disturbances were both the result of a common underlying pathological mechanism. Lennox, one of the proponents of the "period of normality", felt that patients with epilepsy were essentially no different from anybody else; the dominant opinion of this period was that defects of personality or intellect, if they occurred, were due to one or more of the following: structural brain disease, uncontrolled seizures, anticonvulsant drugs, psychological reaction to family and social isolation and rejection. The "period of normality" continues to the present time for people with epilepsy in general. With the advent of the EEG and the recognition of temporal lobe abnormalities, the notion that patients with psychomotor epilepsy displayed specific personality characteristics arose. Today this is an area of controversy.

There are several studies on unselected patients which demonstrate an increased incidence of psychiatric disturbance in both adults and in children with epilepsy, and these are summarised in Table 11.

Although only 2 studies used control groups for comparison, it can be seen that the incidence of psychopathology is high in people with epilepsy, being approximately 2 to 4 times greater than in the general population. Four of the 6 studies found the incidence of psychiatric disorders evident in about one third of all patients.

TABLE 11: STUDIES OF UNSELECTED POPULATIONS OF EPILEPTIC PATIENTS SHOWING PSYCHOPATHOLOGY (From Trimble 1981)

Author		Population	Adults Or Children	Incidence Of Psychiatric Disorder	Control Group
Henderson	1953	Schoolchildren	Children	12%	-
Juul-Jensen	1964	General Population	Adults	35%*	-
Pond & Bidwell	1960	General Practice Study	Adults & Children	29%*	-
Gudmundsson	1966	Iceland Survey	Adults	52%*	-
Rutter et al	1970	Isle of Wight Study	Children	28.6%*	6.6%
Mellor et al	1973	Unselected Schoolchildren	Children	27.0%	15%

*Highest in complex partial seizures

The studies of inter-ictal psychopathology found in people with epilepsy have focussed on several areas, such as personality problems, intellectual deterioration, aggression, sexual dysfunctions, the psychoses and the affective disorders. Most of the areas are controversial and, apart from the affective disorders, will only be mentioned briefly, and the various debates not entered into.

The question as to whether or not a particular type of psychopathology is found in people with epilepsy has been addressed. Pierce Clark (1917) gave a vivid description of the "classical epileptic personality". The Scandinavian school, led by Stromgren (1936), Bingley (1958), Gudmundsson (1966) and Sjobring (1973), used the terms "ixothymic", "ixoid" and "ixophrenic" to describe the viscosity or adhesiveness said to be typical of the epileptic personality. Others, (Pond and Bidwell 1960; Rutter et al 1970), refuted the idea of a special type of psychopathology in people with epilepsy, implying that the psychiatric disturbance covers a similar spectrum as that found in other populations. Several authors have ascribed certain personality traits to people with epilepsy, especially TLE, such as adhesiveness, querulousness, suspiciousness, stubbornness, pedantry, dysphoria, irritability, assertiveness, (Bingley 1958), humourless, sobriety, dependence, obsessionalism, circumstantiality, philosophical interests, anger (Bear and Fedio 1977), hypergraphia, hyperreligiosity and hyposexuality (Waxman and Geschwind 1975; Roberts et al 1982). Stevens (1982) makes the point that many of these perjorative descriptions have not been scientifically substantiated. Recently, Dickman et al (1983) used the Minnesota Multiphasic Personality Inventory (MMPI) and failed to support the

notion of increased psychopathology in persons with TLE. Mungas (1982) administered the Bear and Fedio (1977) inventory to various groups, including one with TLE, one with neurological and behavioural disorders and one with psychiatric disorders: results indicated that the psychopathology reported was not specific for TLE.

Intellectual deterioration has been reported in people with epilepsy, and cognitive functioning may be impaired due to injudicious prescriptions of anticonvulsants, and polytherapy (Thompson 1981), but as can be seen from Table 12, the intelligence quotients of various groups of epileptic populations do not fall into the subnormal range.

It is widely believed that individuals with epilepsy, especially TLE, are prone to impulsive irritable and aggressive behaviour (Pincus 1980). When differences between aggressive and non-aggressive patients with TLE were investigated, aggressivness was associated with early onset of seizures, youth, male sex, low IQ, low social class, an unhappy childhood and an epileptic focus in the dominant hemisphere (Serafetinides 1965; Taylor 1969a). However, a recent review (Kligman and Goldberg 1975) of 8 controlled studies concluded that due to flaws in methodology, no valid conclusions could be drawn regarding the relationship between aggressive behaviour and TLE.

Generally the literature seems to support the notion that people with epilepsy, and especially TLE. show an increased incidence of hyposexuality, sexual hypoactivity, impotence or frigidity (Blumer and Walker 1967; Kolářský et al 1967; Taylor 1969b; Shukla et al 1979).

The relationship between epilepsy, especially TLE, and the schizophrenia-like psychoses of epilepsy are particularly controversial. Hill (1953) and Pond (1957) drew attention to an increased rate of a schizophrenia-like syndrome in patients with TLE. Slater et al (1963) were the first to study the schizophrenia-like psychoses of epilepsy in detail. Of the 69 patients with both epilepsy and psychosis, 80% showed evidence of temporal lobe dysfunction. The patients characteristically had normal premorbid personalities, and, before the onset of psychoses, which occurred after epilepsy had been present for a mean of 14.10 years, there was a reduction in seizure frequency. Affective disturbence of some kind was shown by all patients, especially irritability and depression.

TABLE 12: INTELLIGENCE QUOTIENTS (IQs) OF PEOPLE WITH EPILEPSY

Author(s)	Date	Sample	Mean IQ
1) Somerfeld-Ziskind and Ziskind	1940	100 adults, outpatients	93
2) Collins	1951	400 outpatients	108
3) Zimmerman et al	1951	200 adults	100
4) Davies-Eysenck	1952	161 outpatients, children and young adults	94
5) Vislie and Henriksen	1958	142 outpatients	96
6) Nuffield	1961	288 outpatients, including psychiatric referrals	89
7) Dennerll et al	1964	100 adult outpatients	97
8) Needham et al	1969	22 adults	90
9) Blumer et al	1974	18 temporal lobe epileptics	92.1
		8 generalised epileptics	86.7
10) McIntyre et al	1976	11 patients with right sided temporal lobe foci	102
		11 patients with left sided temporal lobe foci	100
11) Dickmen and Matthews	1977	26 patients, moderate seizure frequency	91
12) Batzel et al	1980	20 employed patients	105
		30 unemployed patients	93

CHAPTER 3

DEPRESSION AND EPILEPSY

The psychoses were characterised by the absence of deterioration, lack of withdrawal, retention of appropriate affective responses and absence of genetic predisposition (Pond 1957; Slater et al 1963; Taylor 1972).

Many other investigators have addressed various questions on the subject. The average interval between onset of epilepsy and psychosis is roughly 13 years (Slater et al 1963; Glaser 1964; Bruens 1971; Kristensen and Sindrup 1978). Several authors have noted a decrease seizure frequency prior to the onset of psychosis (Pond 1957; Flor Henry 1969; Bruens 1971; Sigal 1976; Kristensen and Sindrup 1978; Jensen and Larsen 1979b). The greatest area of controversy is as to whether the schizophrenia-like psychoses are associated with TLE or not: authors in favour of the argument are Slater et al (1963), Bruens (1971), Sigal (1976), Toone and Driver (1980), Ounsted and Lindsay (1981) and Trimble and Perez (1982). Workers refuting the idea are Small et al (1962), Stevens (1966), Mignone et al (1970) and Standage and Fenton (1975). Stevens (1966), for example, has questioned the role played by selective referral to specialist centres. As is pointed out by Toone et al (1982), an unselected sample of an unusual syndrome is hard to come by, and the debate seems likely to remain unresolved. The question of laterality of a lesion and psychopathology will be discussed later.

CHAPTER 3

DEPRESSION AND EPILEPSY

3.1. History and Introduction

A relationship between depression and epilepsy has been described since antiquity. Hippocrates (460-357BC) considered epilepsy and melancholia to be closely related: "melancholics ordinarily become epileptics, and epileptics melancholics: of these two states, what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy" (Lewis 1934a). Temkin (1971) quotes Aretaeus as saying that epileptics were "languid, spiritless..... unsociable, and not disposed to hold intercourse, nor to be sociable, at any period of life; sleepless, subject to many horrid dreams, and without appetite". Paulus Aegineta (625-700) thought that one of the 2 causes of epilepsy was melancholic humour either in the brain or its cavities (Whitwell 1936). Cardanus (1501-1576) wrote about a case of melancholia alternating with epilepsy (Whitwell 1936), an interesting forerunner to the authors who have described a reduction in seizure frequency heralding the onset of a depressive illness in patients with epilepsy. Griesinger (1857) noted that a "misanthropic perversion of sentiment, sometimes even actual melancholia with suicidal tendency is observed in a great many epileptics".

Nearer our own time Barham (1907) and Baugh (1908) described the epileptic populations in psychiatric hospitals in Britain, and the only mental disorders mentioned in connection with epilepsy were melancholia and mania. White (1900), describing the City of London asylum, made the observation that fits occurring spontaneously in the course of mania or melancholia might lead to recovery from these conditions, an interesting pre-ECT idea. Jones (1912) suggested that one third of the people with epilepsy in Britain at that time were also "insane". He also made the interesting observation, which had been made by the previous authors, that "when epilepsy is associated with insanity, the tone of the mental condition is that of depression or melancholia rather than that of mania".

In addition, a number of earlier authors commented on acute changes in the mental state that were observed in epileptic patients which included over-excitement, mania and depression. These latter changes, which may be defined as peri-ictal, fit into our present classification of the relationship between epilepsy and psychiatric disturbances, dividing them into 2 main categories. There are those that occur around the ictus,

including prodromata, ictal and post-ictal disturbances, which may be grouped together as peri-ictal events. On the other hand, there are those which are inter-ictal, in which the psychiatric disturbances are chronic, and are now shown to be directly related to the ictal electrical disturbances. With regard to depression, this same classification is used.

3.2. Clinical Syndromes

3.2.i. Peri-ictal depression

Many patients complain of prodromal symptoms which may last for days before an ictus, including feelings of dysphoria, irritability and depression. This state is of interest, because in some patients the discomfort is relieved by the epileptic attack; of importance is that some patients seem to need to have their seizures, and that increasing the anticonvulsant medication may exacerbate the dysphoria, by diminishing seizure frequency. Affective feelings, including both euphoria and depression, have been noted as ictal symptoms, presenting in some patients as an aura.

Russel Reynolds (1861) was one of the first to describe the syndrome, when he mentioned sudden depression of spirits as part of an epileptic aura.

Mulder and Daly (1952) described the psychiatric symptoms of 100 non-institutionalised patients who had lesions of the temporal lobe, and whose presenting complaints were usually thought to be psychiatric. Fifteen patients experienced ictal mood changes which included 10 who complained of dread, terror, anger or overwhelming fear. The remainder had a feeling of well being. Weil (1955; 1956) described ictal depressions in 6 and 7 patients respectively, who suffered from temporal lobe automatisms with uncinate attacks. The odours were universally described as unpleasant ones. Depressive episodes lasted from several minutes to 14 days. Williams (1956) studied 100 patients who felt an emotion as part of the epileptic experience. They were found in about 2000 patients living at home, half seen as hospital out-patients and half in a private practice. Sixty one (3%) experienced ictal fear and 21 (1%) depression. Of the 61 patients with ictal fear or anxiety, 52 had temporal lobe foci. The severity of the depression ranged from mild to severe, and in 5 patients suicidal ideation occurred; one of

the 5 attempted suicide, while another committed suicide. The author found that the ictal depression lasted longer than other epileptic experiences, and in 8 of the cases, the changes lasted longer than a day. Weil (1959) studied a group of 132 subjects with temporal lobe seizures and noted that 28 patients (21%) experienced "ictal emotions" of which half of these (14 patients) had ictal depression, which was characterised by "sudden let-down of mood and psychomotor retardation" and may result in suicidal attempts. Betts (1982) described a patient who cut his throat whilst in an ictal depressive state.

Wells (1975) described a patient who presented with psychotic depression, and whose EEG record at the time disclosed frequent bursts, usually lasting 5 to 7 seconds, of high amplitude, rhythmical, bilaterally synchronous 2 cps spike and wave activity; the discharges were continuous enough to justify the diagnosis of status epilepticus. Two patients have been described who presented with depressive symptomatology during petit mal status (Tucker and Forster 1950; Jaffe 1962). Henriksen (1973) described affective disturbances in association with partial seizure status. He reported a 41 year old right handed woman with a long psychiatric history of anxiety and depression. During a prolonged state of anxiety at the age of 39 she experienced frequent bouts of fear and during this period nearly continuous spiking was recorded in the right sphenoidal lead. After a right temporal lobectomy, the bouts of fear did not recur and spiking on the EEG was absent.

Freedman et al (1976) stress that the "psychic seizures" which seem to be primarily of temporal lobe origin may occur without loss of consciousness or, less commonly, precede a generalised convulsion; these can present as acute paroxysmal feelings of despair and depression, with or without suicidal ideation. Feelings of pleasure, elation, or serenity are somewhat rarer.

3.2.ii. Inter-ictal depression

It is important to distinguish between misery and sadness and a depressive illness which, according to some, may be further divided into endogenous depression and non-endogenous depression (also called neurotic or reactive depression). It is understandable that most patients on being given a diagnosis of epilepsy go through a period of sadness and adjustment, but after "working through" this period will tend to return to normal mood. In some patients, however, depressive symptoms may occur as part of a depressive illness (See page 20).

The prevalence of depression in epilepsy is unknown. Although there have been several investigations as mentioned earlier indicating that patients with epilepsy have a higher psychiatric morbidity than patients without, depression in general was not a feature selected for analysis in the surveys. Review of the modern literature gives the impression that depression is perhaps the commonest major psychiatric complication of epilepsy, yet it has not been well investigated.

Mulder and Daly (1952) described inter-ictal psychiatric disturbances in 62 patients. The most common symptom was anxiety, which was present in 36 patients and was evidenced by insomnia, irritability and somatic manifestations. Depression was the next most common symptom and occurred in 16 patients. The authors remarked that the depression was "reactive", and the only difference from anxiety was one of degree, as they felt the "mechanisms of formation of the symptoms appeared to be much the same".

Several studies employing the MMPI have shown the depression scale to be raised in patients with epilepsy (Guerrant et al 1962; Meier and French 1965), while others have shown it to be the most elevated scale for people with epilepsy overall and/or the most elevated scale across individual profiles (Modlin 1960; Kløve and Doehring 1962; Matthews and Kløve 1968; Glass and Mattson 1973). Mignone et al (1970) showed the average MMPI scores for all scales of their entire epileptic group were significantly higher than those of a large control population. In addition, the depression scores were higher for late onset fits of whatever kind than for early onset fits. Rodin et al (1976) used the MMPI to compare a group of 78 patients with TLE with an age, sex & IQ matched group of patients having other types of seizures. The TLE group had higher scores on depression. Recently, Dickmen et al (1983) evaluated the use of the MMPI in research in psychopathology of people with epilepsy, and concluded that it was a sensitive and valid instrument. Moreover, they found that the Depression Scale of the MMPI was significantly higher in patients with partial complex seizures with secondary generalisation, when compared to those with primary generalised convulsive seizures.

Several clinical investigations have also noted high incidence of affective disturbances in patients with epilepsy. Dominian et al (1963) reported depression to be the most common psychiatric symptom occurring in patients with late onset epilepsy, being found in a total of 13 out of 51 patients (25%). Moreover they found that 8 of the 13 depressives (61%) showed a premorbid affective disturbance of depression. Currie et al (1971) found anxiety and depression to be the most frequent psychiatric abnormalities

among 666 persons with TLE, occurring in 127 (19%) and 71 (11%) respectively. It is of interest to note that in 48 (7%), the symptoms of anxiety and depression antedated the first attacks of epilepsy. Dalby (1971) noted that in a group of 93 patients with psychomotor epilepsy, 54 patients (58%) were psychiatrically abnormal. Twenty-five patients had "non-phasic character changes" which included some with affective over-reaction to trivial situations and depressive neurotic traits. Twenty-four patients had "episodic" mental changes of which 18 (75%) had periodic depression with endogenous features, and 2 had episodes of manic psychosis. Taylor (1972) noted that depression and anxiety were very common in patients with TLE referred for surgery. He made the point that the depression, in the sense of unhappiness, sadness and a mood of discontent, was of moderate degree, fluctuating in both depth and time, and was often accompanied by free-floating anxiety. Mellor et al (1974) described children with epilepsy as being particularly prone to depression.

Hancock and Bevilacqua (1971) described 4 female patients who had feelings of anxiety, depression, suicidal ideation and/or attempts associated with, at times, dizziness, amnesias, vertigo, tinnitus and/or headaches. Neurological examinations were essentially normal, but all patients had abnormal EEGs localised to the temporal lobes. The importance of anticonvulsants as part of successful therapy was emphasised.

Betts (1974) studied 72 patients with epilepsy admitted to a psychiatric hospital and found that depression was the commonest psychiatric diagnosis, being found in 22 patients (31% of the sample). This study was the only one to differentiate between the types of depression and it was noted that of the 31% depressed patients, 12 (17%) had clinically been diagnosed as having endogenous depression, while 10 (14%) had had reactive depression.

Gunn (1977) found depression to be the most common psychiatric abnormality in a group of 158 prisoners with epilepsy. Mild depression was found in 19 (12%) while moderate depression was found in 34 (22%), as compared with the figures of 16% and 11% respectively with controls.

Standage and Fenton (1975) compared the mental state of patients with chronic epilepsy and controls with locomotor disorders, who were diagnostically heterogeneous but were individually matched with the epileptics for sex, age and duration of illness. Both groups of patients were rated on the Present State Examination (PSE)*. Somatic symptoms of depression were found in approximately 60% of the patients with epilepsy, while in only 30% of the control subjects. Depressive mood was the most common symptom in the epilepsy group, occurring in about 75%.

*Wing et al (1980)

Bear and Fedio (1977), constructed their own scale of 18 traits supposedly associated with inter-ictal behaviour, and tested 27 patients with unilateral TLE, comparing them with a group of 12 normal adults and a group of 9 patients with neuromuscular disorders. They found more self-reported depression in persons with TLE.

Trimble and Perez (1980) used the Middlesex Hospital Questionnaire (MHQ) now known as the Crown-Crisp Experiential Index (CCEI) to assess the phenomenology and frequency of psychiatric illness in a group of 281 adult non-psychiatrically selected patients with epilepsy admitted to a centre for epilepsy, either for evaluation of their epilepsy, control of seizures, or rehabilitation. As a whole, the group were noted to have higher anxiety and depression scores than a control, normal population, and the mean depression score was found to be equivalent to that found in a psychiatric out-patient population. In that study no direct relationship between the type of epilepsy and the depression was discovered.

Toone and Driver (1980) described affective psychoses in 15 (36.6%) of their sample of 41 psychotic patients with epilepsy.

Kogeorgos et al (1982) assessed the psychiatric morbidity of a group of 66 chronic epileptic patients attending a neurological out-patient clinic and unknown to psychiatric agencies using the General Health Questionnaire and the CCEI, and compared them with 50 consecutive non-epileptic neurological control out-patients who met similar inclusion and exclusion criteria. Nearly half (45.5%) of the epileptics were classified as probable psychiatric cases. Psychiatric morbidity was both more prevalent and severe in this group than in a comparison group of chronic neurological out-patients. Depression, anxiety and hysterical symptomatology were the most common characteristics of the psychiatrically impaired patients.

Betts (1981) describes the endogenous type of depressive illness in someone with epilepsy as having a sudden onset and sudden departure; its severity may also fluctuate quite markedly whilst it is present.

Manic psychoses are uncommon in epileptics. Wolf (1982) reviewed the literature and found only 9 case studies of mania in people with epilepsy. He reported an additional 6 patients with manic syndromes; one patient had generalised epilepsy and 5 had TLE. In 3 of the patients it was felt that the manic states were part of the epileptic process, as they were closely linked to dynamic phases of the seizure disorder. Of these, one had a post-ictal psychosis, while 2 were associated with decreased

seizure frequency, one showing "forced normalisation". In 2 cases, the seizures had long been controlled and there was no change in medication when they had the first psychotic phase: the symptomatology was indistinguishable from a functional manic psychosis. The final patient had a bipolar affective disorder which preceded his first seizure by 3 years.

Recently, Toone et al (1982) conducted a retrospective investigation on 69 patients with a combined diagnosis of epilepsy and psychosis, and compared them with 53 patients with a diagnosis of functional psychosis. The "epileptic affective patients" in their series often lacked convincing psychotic features, and it was concluded that they did not appear to form a distinctive syndrome, and that the occurrence might well represent a chance association. Only 3 patients showed evidence of bipolarity. Mutiple episodes occurred more commonly in the index group.

3.3. The Relationship of Mood to Seizure Frequency

Several authors have noticed a decreased seizure frequency heralding the onset of a depressive illness. Weil (1956) described depressive episodes which occurred paroxysmally in the "free interval" between temporal lobe seizures. Dongier (1959/60) noted that patients whose EEG "normalised" during a psychotic period were frequently depressed. James (1960), and Falconer and Serafetinides (1963) both reported depressive illness in patients whose seizures had declined as a result of temporal lobectomy. The data of Flor-Henry (1969) suggest that the affective psychoses are correlated with major convulsive epilepsy and that the onset of depression seemed to be associated with a significant reduction in the patient's usual seizure frequency. Betts (1974) found that a decline in attack frequency was significantly associated with a diagnosis of endogenous depression. He found a significant association between a 50% reduction in seizure frequency before admission to hospital in patients admitted with depressive illness, while an increase in seizure frequency was common in those epileptic patients admitted with either acute behaviour disturbance or clouded states. Standage and Fenton (1975) in their study found that epileptics scored higher on various items including somatic symptoms of depression and depressive mood. They found that, in addition, a significantly higher proportion of the "high scoring" group had experienced fewer attacks than usual in the month before examination.

3.4. Suicide and Epilepsy

Esquirol in 1845 and Gowers in 1901 noted an association between epilepsy and suicide.

A patient with epilepsy might be at a high risk from suicide for several reasons. Firstly, epilepsy brings social handicaps (Pond and Bidwell 1960) such as housing difficulties, schooling, employment and problems with interpersonal relationships. Secondly psychiatric disturbance is common among people with epilepsy, as has been discussed earlier, and this may predispose to suicidal behaviour. Thirdly, is it the dysfunctional epileptic mechanism per se at fault, or the dysphoria associated with epilepsy? Finally, Trimble and Reynolds (1976) pointed out that anticonvulsant drugs themselves may be depressant, barbiturates being the worst offenders.

Sudden, unexplained death is frequent in persons with epilepsy. Krohn (1963) found that bronchopneumonia, sudden death and accidents caused more than half of the deaths in epileptics. However, many accidents are not accidents at all, but are caused by the victim's own disposition. Suicide carries with it a stigma, so sudden, accidental or death due to undetermined causes may be given as verdicts instead of suicide. The mortality rates and causes of death in patients with epilepsy vary according to the sources of data. Kurtzke, cited in Zieliński (1974) pointed out that death certificates are apt to reveal only those patients whose epilepsy was the primary cause of death. For these reasons, the figures given for the frequency of suicidal behaviour in epileptics may well be an underestimation.

Jay and Leestma (1981) comprehensively reviewed the literature and statistics relating to death in epilepsy and indicated that between 3% and 31% of recorded cases, death is sudden, unexpected, and at autopsy no apparent pathological basis for death is found. The authors postulated that pathophysiological mechanisms, including cardiac arrythmias are responsible for many deaths, and it is as well to bear this in mind, so as to gain perspective when considering suicide in epilepsy,

Exact figures of suicide, and even more so of parasuicide among people with epilepsy are difficult to obtain. In the epilepsy literature from 1940 to date, it is possible to derive some evidence about the incidence of suicide and parasuicide, sudden or accidental deaths amongst patients with epilepsy.

Some authors (Batchelor 1954; Burston 1969) do not recognise epilepsy as a significant concomitant of self poisoning. They are, however, the exception.

Mathews and Barabas (1981) reviewed the literature on epilepsy and suicide, and Table 13 shows the results of their findings.

TABLE 13: SUICIDE AMONG EPILEPTIC PATIENTS

(After Mathews and Barabas 1981)

Investigators	Years	Deaths (Number)	Suicides (Number)	Deaths By Suicide (%)
Bridge	1949	45	1	2.2
Lennox and Lennox	1960	118	11	9.3
Krohn	1963	107	3	2.8
Freytag and Lindenberg	1964	294	9	3.1
Penning et al	1969	171	4	2.3
Sillanpää	1973	18	1	5.6
Zieliński	1974	218	16	7.3
Iivanainen and Lehtimen	1979	179	13	7.3
Average based on studies above				5.0
Average based on studies of general population				1.4

Of the 1150 deaths of epileptics represented in the mortality studies cited, an average of 5.0% of the deaths resulted from suicide, whereas the suicide rate in the USA general population is 1.4%. This indicates a four-fold increased risk of suicide in people with epilepsy. However, there were methodological problems, particularly the lack of group comparability, as the studies came from several countries, while the general population estimate was from the USA.

Barraclough (1981) also reviewed the literature on epilepsy and suicide. Only 2 papers in his review had been included in the work of Mathews and Barabas (1981). Barraclough, in addition, approached the subject from a slightly different angle. A paper was included if the number of suicides and the expected number was given, or enough information to make an estimate. He calculated an expected number by multiplying together the

TABLE 14: FOLLOW UP STUDIES OF PATIENTS WITH EPILEPSY, REPORTING MORTALITY FROM SUICIDE (After Barraclough 1981)

Author	Year	Country	No. of Suicides Obs.	Exp.	No. of Dead		% of Deaths From Suicide		Sample Size	Follow Up Period
Temporal Lobe Epilepsy										
Currie et al	1971	England	3	0.3*	54	(12)	6	(25)	493(a)	1-25 yrs
Stépien et al	1969	Poland	2	0.03	3	(2)	67	(100)	77	1- 9 yrs
Lindsay et al	1979	England	1	0.05	9	(6)	11	(17)	100	12-29 yrs
Taylor and Marsh	1977	England	9	0.2	37		24		193	5-24 yrs
Epileptics in Institutions										
Prudhomme	1941	USA	8	1.7	1100		0.7		several thousand	14 yrs
White et al	1979	England	21	3.9	636	(425)	3	(5)	1980	6-27 yrs
General Hospital Patients										
Dalby	1969	Denmark	2	0.2	10		20		346	4-16 yrs
Henriksen et al	1970	Denmark	21	7	104	(79)	20	(26)	2763	25 yrs
Sillanpää	1973	Finland	1	0.001**	18		6		245	10 yrs
Zieliński	1974	Poland	16	2†	218		7		6710	3 yrs
Life Insurance										
Society of Actuaries	1954	USA	2	0.7	157		2		1000	1-15 yrs

Glossary of Symbols for Table 14

(...) Figures in brackets are deaths unrelated to epilepsy or its treatment.

* Expected number based on sample size and follow up period applying national suicide rate; all other expected numbers calculated by the authors of the paper in question.

** Because original sample were children.

/ Calculated from author's statement that suicide was 5 times commoner in men and 10 times commoner in women.

(a) Patients aged 15 and over from sample of 666.

TABLE 15: SUMMARY OF PAPERS REPORTING SUICIDE IN PATIENTS WITH EPILEPSY

(From Barraclough 1981)

	No. of Papers	Observed Suicides	Expected Suicides	O/E
Temporal Lobe Epilepsy	4	15	0.6	25
Institutions	2	29	5.6	5
General Hospitals	4	40	9.2	4
Insurance	1	2	0.7	4
TOTAL	11	86	16	5

numbers of persons in the cohort, the mean years of follow-up and the suicide rate of that country. He pointed out that the difference between observed and expected numbers is minimised by this method, because the cohorts of people with epilepsy are on average younger than the general population to whom national suicide rates apply. The author found 11 papers and these were divided into 4 groups. There were 4 papers about TLE, 2 studies on epileptics who resided in institutions, 6 articles about people with epilepsy who had been referred for diagnosis and treatment in general hospitals as in-patients or as out-patients, and lastly, a paper based on life insurance statistics. For details of the papers refer to Tables 14 and 15. Barraclough (1981) concluded his review by summing the observed and expected values to estimate what increased risk epilepsy has for suicide. There were 86 suicides and 16 expected, which gives an increased risk of suicide of approximately 5. The highest increased risk was associated with TLE, being approximately 25 times the expected.

One more report, not discussed, Hauser et al (1980), determined the standardised mortality ratios (SMR) for a cohort of 618 patients with a diagnosis of epilepsy, and residents of Rochester, Minnesota, between 1935 and 1974. The SMR was significantly increased from the expected, in that there were 185 deaths with 81.9 expected. There were 3 suicide deaths in the cohort. This number was not increased above that expected. However, there was a significant excess of deaths due to accidents in the series: 12 deaths were observed and only 4.9 expected.

In conclusion, it would appear that the mortality of people with epilepsy is increased. The suicide rate for people with epilepsy is at least 4 to 5 times higher than that of the general population, but in the case of people with TLE, the risk is about 25 times greater. Sudden, unexplained deaths and accidents are also frequent in people with epilepsy. Some of these may well be suicides. Suicide, however, could be the manifestation of an uncontrolled impulsivity, a depressive illness or a psychosis.

3.5. Parasuicide in People with Epilepsy

Delay et al (1957) draw attention to the difficulties of distinguishing between true suicide, self-mutilation and accidental death in the epileptic. Even so, looking at attempted, rather than completed suicide, they estimated that of their series of 347 epileptic patients, about one third made one or more suicidal attempts.

Harrington and Cross (1959) reported 6 people with epilepsy out of 102 patients attempting suicide, while Sclare and Hamilton (1963) cited 5 epileptics in 45 cases of parasuicide. Both these figures are somewhat lower than those of Delay et al (1957) whose figure of 30% of epileptic patients attempting suicide was confirmed by Barande, cited in Gunn (1977), who studied 94 epileptics in a prison and contrasted them with 65 in a mental hospital, and also came to the conclusion that about one third of the people with epilepsy in his sample had made suicidal attempts. Out of 69 psychotic patients with epilepsy studied by Slater et al (1963), 17 (25%) attempted suicide. Jensen and Larsen (1979a) followed up 74 patients after resection of a temporal lobe and 14 of those (19%) attempted suicide on one or more occasions.

Mackay (1979) conducted a prospective hospital based study which described the characteristics of epileptic patients who presented themselves as self-poisoners at the Glasgow Western Infirmary and compared them with an age and sex matched group of self-poisoners who did not suffer from epilepsy. From 1972 to 1976, 130 people with epilepsy presented 171 times to the hospital as medical emergencies with self-poisoning. They constituted 3.5% of 3733 patients poisoning themselves on 4121 occasions. Taking the incidence of epilepsy in the general population as 0.4% (Bannister 1973), such patients occurred 7 times more commonly than expected. Repetition of self-poisoning was more common in this population (18.5%), than in those without fits (7%). More than 2 episodes of poisoning in a 12 month period was also common in epileptics. In addition, less alcohol excess at the time of the act was found in the index group, but more psychopathy was evident.

Hawton et al (1980) looked at the association between epilepsy and attempted suicide in the Oxford area. In a 2 year study of patients admitted to hospital after deliberate self-poisoning or self-injury, a five-fold excess of patients was found compared with the general population prevalence rates. Males with epilepsy were particularly over-represented,

and patients with epilepsy were prone to make repeat attempts. Anticonvulsants, particularly the barbiturates, were used in most cases of self-poisoning which accounted for 84% of attempts. Barbiturates were used in 60% of the anticonvulsants used. Thirteen percent had presented with self-injury, while 4% had employed both methods.

Sclare and Hamilton (1963) studied in detail 180 randomly referred cases of attempted suicide in Glasgow. This paper is helpful in gaining perspective as to the conditions associated with parasuicide especially to compare other chronic conditions with epilepsy. Previous psychiatric illness was found in every case, while physical illness was associated in 26% of cases. A breakdown of these showed that:
15 cases (34%) had respiratory illness
5 cases (11%) had epilepsy
5 cases (11%) had cardiovascular illness
2 cases (4%) had an ulcer, while the remaining
18 cases (40%) were made up of isolated various physical conditions

In conclusion, it does appear that physical illness including epilepsy, is associated with an increased risk of parasuicide. In the group with epilepsy, repetition of self-poisoning seems common, and overdosage with anticonvulsants, particularly the barbiturates, appears to be a method frequently employed.

3.6. Treatment of Depression in Patients with Epilepsy

Literature to date suggests that virtually all non-MAOI antidepressants and some MAOI antidepressants lower the seizure threshold, although not to the same degree, and may therefore provoke seizures clinically (Trimble 1978b; Edwards 1979; Trimble 1980; Edwards and Glen-Bott 1983). Drugs particularly implicated (See Table 16) include maprotiline, mianserin, amitriptyline, clomipramine and imipramine, some of the most widely used antidepressants. The figures in the table give some idea of the epileptogenic potential of antidepressants, but should be interpreted with caution, as only about 10% of adverse reactions are reported to the CSM (Dunlop 1971), from which much of the information about the incidence of side-effects and convulsions is obtained.

TABLE 16: CONVULSIONS IN PATIENTS ON ANTIDEPRESSANTS

(Adapted from Edwards 1979; Edwards and Glen-Bott 1983)

Antidepressant	Year Introduced(1)* Into UK	Number of Cases Convulsions-CSM (December 1980)	Deaths (1979)	% Prescriptions Of Market Share (1979)
Maprotiline	1975	117		3.6
Mianserin	1976	40		5.8
Amitriptyline	1961	37		34.2
Clomipramine	1970	25		5.5
Imipramine	1959	18	2	13.5
Nortriptyline	1963	13	1	2.2
Dothiepin	1969	12		13.3
Trimipramine	1966	12	1	7.1
Flupenthixol	1973	10		....
Desipramine	1962	8	1	....
Lithium	1964	7	1	2.2
Viloxazine	1974	6	1	....
Phenelzine	1959	5		1.3
Doxepin	1969	4		3.9
Tranylcypromine	1960	4		0.3
Dibenzepin	1970	3		....
Protriptyline	1967	3		0.5
Iprindole	1968	2		0.3
L-Tryptophan	1971	2		1.3
Lofepramine	1983	2(1)*		....
Zimelidine	1982	1(2)*		....
Butriptyline	1975	0		....
Iproniazid	1957	0		....
Isocarboxazid	1960	0		0.3
Nomifensine	1977	0		2.6
Opipramol	1971	0		....
Tofenacin	1971	0		....
		Total 331		

References: (1)* From Pharmaceutical Companies
(2)* Simpson et al 1981
Shares marked .... total less than 1.4% between them

NB Amoxapine, not on the UK market, has caused convulsions in 3 patients who took an overdose (Bock et al 1982; Golberg and Spector 1982, cited by Bock et al 1982).

Zimelidine, one of the newest antidepressants, has been known to produce a convulsion in a person without epilepsy who took an overdose (Simpson et al 1981). Convulsions have also been reported in 2 patients receiving therapeutic doses of lofepramine, a TCA introduced onto the UK market in 1983; one patient had a history of epilepsy, while the other was on concomitant amitriptyline therapy (E. Merk Limited - personal communication, 1983).

Betts et al (1968) and Dallos and Heathfield (1969) first made the point that even in therapeutic doses the TCAs may increase seizure susceptibility, especially in predisposed individuals, such as those with a family history of epilepsy, pre-existing brain damage and a history of previous ECT. Paradoxically, however, there is a suggestion that some TCAs may have a therapeutic effect on generalised absence seizures in children (Fromm et al 1978).

Nomifensine, on the other hand, has been suggested to not lower and possibly even raise the seizure threshold, and may therefore prove of value in the management of depression in patients with epilepsy (Nawishy et al 1980).

When various drugs are administered to a patient, there are pharmacokinetic interactions which may alter the efficacy and/or side effects of the other agents. Table 17 shows some important pharmacokinetic interactions affecting the major anticonvulsants. Two effects will be considered: firstly, the effect which antidepressants have on anticonvulsants and secondly the effect which anticonvulsants have on antidepressants.

Houghton and Richens (1975) treated 5 epileptic patients with nortriptyline 75mg/day which caused a small, but insignificant, increase in their serum DPH levels. Lipman (1975) reviewed the occurrence of drug interactions between barbiturate anticonvulsants and some TCAs, namely amitriptyline, nortriptyline and desipramine, with possible diminution of antidepressant activity due to enhanced metabolism caused by the barbiturates. He reported that overdoses of doxepin, imipramine and protriptyline potentiated intoxication of barbiturate anticonvulsants. Perucca and Richens (1977) reported DPH intoxication in 2 epileptic patients who were receiving imipramine 75mg/day.

TABLE 17: SOME IMPORTANT PHARMACOKINETIC INTERACTIONS AFFECTING THE MAJOR ANTICONVULSANTS

(Adapted from Sutherland and Eadie 1980, unless otherwise indicated)

Anticonvulsant	Drugs Raising Plasma Levels of the Anticonvulsant	Drugs Lowering Plasma Levels of the Anticonvulsant
Phenytoin	Sulthiame Ethosuximide Valproate Imipramine[1] Nortriptyline[3] (NS)	Carbamazepine Clonazepam Folic Acid
Carbamazepine		Phenytoin Phenobarbitone Primidone[2]
Phenobarbitone	Phenytoin Valproate Doxepin[4] Imipramine[4] Protriptyline[4]	
Valproate		Phenobarbitone ? Phenytoin
Clonazepam		Phenobarbitone Phenytoin

References: 1 = Perucca and Richens 1977
2 = Eadie and Tyrer 1980
3 = Houghton and Richens 1975
4 = Lipman 1975

Hammer et al (1967) reported a fall of about 50% in the steady state plasma desipramine levels in one patient who was given PB. Alexanderson et al (1969) found that volunteer subjects receiving barbiturates had lower steady state nortriptyline levels than control subjects who had not been taking barbiturates. MacCallum (1980) reported that substitution of DPH with CBZ in a manic depressive patient who was receiving lithium resulted in the disappearance of the clinical signs of lithium intoxication: these findings were interpreted as evidence that DPH potentiated the toxic effects of lithium.

In a recent investigation (Nawishy 1982), depressed epileptic patients were treated with nomifensine or mianserin and only insignificant changes in DPH or PB levels occurred. In a second study, a single oral dose of nomifensine or mianserin was given to epileptic patients receiving anticonvulsant drugs and normal volunteers. Results showed significantly lower levels of both mianserin and nomifensine in the epileptic patients compared to the normal volunteers.

Chadwick et al (1978) treated epileptics with antidepressants, and found that the administration of L-Dopa, L-Tryptophan, MAOIs or MAOIs plus L-Tryptophan did not significantly alter serum anticonvulsant levels of PB, PR, or DPH, but serum levels of CBZ were significantly lower following MAOIs and MAOIs plus L-Tryptophan.

Instead of prescribing antidepressants, an alternative method of alleviating depressive symptomatology in the epileptic may be by altering the anticonvulsants. Thompson and Trimble (1982) assessed a group of patients who underwent a reduction in the number of different anticonvulsant drugs prescribed from a mean of 2.8 drugs to a mean of 1.6 drugs. Results showed that a reduction in polypharmacy significantly reduced anxiety and depression scores on various mood rating scales.

Another possibility of treating the depressed epileptic is with CBZ. Carbamazepine is an effective anticonvulsant and no statistically significant differences have been demonstrated in the efficacy of different anticonvulsants, including CBZ, on major epileptic seizures (Sillanpää 1981). All the anticonvulsants have been shown to impair or have no effect on the cognitive functions of patients with epilepsy (Thompson 1981). Carbamazepine, on the other hand, has been shown by several authors to improve cognitive function (See Table 18). It has been reported by some to have little or no effect on cognitive

function (Rom et al 1967; Rett 1976; Hamster and Petruch 1978). On reviewing the literature there are no reports of CBZ leading to impaired cognitive function (Thompson 1981).

TABLE 18: SOME STUDIES SHOWING THE IMPROVEMENT OF COGNITIVE FUNCTION IN PATIENTS TREATED WITH CARBAMAZEPINE

Author	Date	Sample	Control	Duration Of Treatment	Daily Dose
Martin et al	1965b	20 epileptic children	No	6 months	600mg
Leder	1970	20 epileptics	Yes	12 weeks	600-1000mg
Krasovsky et al	1972	38 behaviourally disturbed children	No	9 weeks	100-600mg
de Weis et al	1974	33 behaviourally disturbed children	Yes	12 weeks	300mg
Dodrill and Troupin	1977	40 epileptics	Yes	8 months	not stated
Schain et al	1977	45 epileptic children	No	4-6 months	8-45mg/kilo
Jacobides	1978	46 epileptics	No	1 year	10-25mg/kilo

Moreover, in a double-blind placebo controlled study on healthy subjects, after the ingestion of CBZ, they were more "confident", in addition to an improvement in manual dexterity (Schmocker et al 1976).

In addition, in controlled clinical studies on normal volunteer populations, Thompson et al (1980) noted significant and dose related impairment of cognitive functioning in volunteers treated with DPH, while the effects during CBZ were insignificant. Moreover, those on CBZ reported themselves to be more active, less depressed and less tired, in contrast to those on DPH who were more fatigued, depressed and less active.

Not only has CBZ been shown to improve cognitive function, but there have been at least 65 reports showing the drug to have a psychotropic effect, while only half a dozen or so fail to show this (Sillanpää 1981). Table 19 shows the controlled studies demonstrating the psychotropic effects of CBZ, and this is possibly because its structure, namely tricyclic, resembles that of the TCA, imipramine (Arieff and Mier 1966; Sillanpää 1981).

TABLE 19: CONTROLLED STUDIES SHOWING PSYCHOTROPIC EFFECT OF CARBAMAZEPINE

Author	Date	Sample	Control Drug
Rajotte et al	1967	24 epileptics with behavioural disorders	Phenytoin
Marjerrison et al	1968	21 epileptics with psychosis	Phenemal
Groh et al	1971	20 behaviourally disturbed children	Placebo
Puente	1976	27 behaviourally disturbed children	Placebo
Dodrill and Troupin	1977	40 epileptics	Phenytoin
Ballenger and Post	1978	8 manic depressives 2 schizoaffective	Placebo
Okuma et al	1979	60 manics	Chlorpromazine

Considerable momentum is growing for the use of CBZ in psychiatric disorders. One of the earliest investigations of the efficacy of CBZ in psychiatry was the study of Alnaes (1965) who gave CBZ to 14 institutionalised epileptics with psychiatric disturbances: it was concluded that in 10 out of the 14 cases, the CBZ improved the mental state of the patients. Daneel (1967) investigated 38 institutionalised epileptics, 26 for psychiatric reasons and 12 because of mental subnormality. When treated with CBZ, marked general behavioural improvement was seen in

18 patients and some improvement in 13 patients: they became more friendly and sociable, less aggressive, and reported to feeling better generally. Pereira (1969) investigated 26 children exhibiting EEGs with paroxysmal abnormalities, without any convulsive history, but manifesting various behavioural disturbances. The children were treated with CBZ and followed up for 6 to 17 months: results showed excellent response in 6 patients, partial in 13 and none in 7. There have been several open studies and case reports on the beneficial effects of CBZ in patients with manic-depressive psychosis and the effects seen were both antimanic, antidepressant and prophylactic (Okuma et al 1973; Folks et al 1982).

Ballenger and Post (1978) reported a double-blind placebo controlled trial involving 10 manic-depressive patients, in which 7 patients improved on CBZ, the effects being antimanic in 3 patients, antidepressant in 3 patients, and both antimanic and antidepressant in a patient with severe mood fluctuations. Okuma et al (1979) carried out a multi-institutional controlled, double-blind study on 63 patients, comparing the antimanic efficacy of CBZ and chlorpromazine. The overall improvement rate, based on the number of cases showing moderate to marked amelioration of manic symptoms was 70% in the CBZ group and 60% in the chlorpromazine group: no significant differences were found between the 2 groups. The onset of effect was seen within 10 days in two thirds of the CBZ group and half of the chlorpromazine group. The incidence of side effects was significantly lower in the CBZ group.

In summary, it seems that instituting monotherapy, especially with CBZ, may be a possible way of treating the depressed epileptic.

Betts (1981) makes the point that epileptic depression can be rather resistant to conventional antidepressant treatment, and may need ECT to clear it. An important part in the management of depression in people with epilepsy is psychotherapy. Depressive symptoms that seem to be reactive either to the diagnosis of epilepsy itself, or to the life circumstances caused by the epilepsy require social work intervention, supportive psychotherapy and possibly even behaviour therapy (Betts 1981).

CHAPTER 4

LATERALITY

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LATERALITY

4.1. Introduction

The problem of localising lesions which result in psychiatric disturbances has occupied much of the literature, but, despite this, the subject remains one of debate and controversy. This is even more true of the present time, as the notion of functional disturbances, such as faulty neurotransmitter mechanisms becomes more popular. With respect to localisation of function and dysfunction in the brain, there are 2 general propositions. The first, which holds that function can be localised within the brain, stems from the early phrenology of Gall, and expanded with the work on aphasia. Among contemporary investigators holding this "localisation" point of view, the contention is that lesions of particular areas of the brain are almost invariably associated with specific dysfunctions.

The alternative view, that the brain operates as a whole, which is more than a mere sum of its separate parts, began with Flourens, a rival of Gall's, and today has numerous exponents. This view is one of equipotentiality which describes "flexibility of brain function in the supposition that the activities of specific areas need not remain fixed and static" (Dimond 1978).

Zangwill (1963) reviewed the history of cerebral localisation of psychological function, and outlined the suggestions of Bouilland who, in 1825, drew attention to the apparent link between loss of speech and lesions of the anterior lobes of the cerebrum; Broca, who in 1861 announced his discovery that the centre for speech is located in the third left frontal convolution and Wernicke's description in 1874 of sensory aphasia related to disease of the left temporal lobe. Hughlings Jackson stood alone, repeatedly warning his colleagues that localisation of a defect is not the same as localisation of a function.

Some modern work on laterality of lesions and psychiatric sequelae is fairly substantial and has come from 2 main sources:

1) Experimental work and neuropsychological testing

2) Clinical studies on neuropsychiatric patients
   a) Studies performed on patients with head injuries
   b) Work on schizophrenic patients
   c) Work carried out on depressed patients
   d) Investigations on patients with epilepsy, which includes:
      Aggression and behaviour disturbances
      Prognosis studies
      Psychoses, affective disorders and neuroses
      Miscellaneous neuropsychiatric disorders

4.2. Review of Studies of Laterality

4.2.i. Experimental work and neuropsychological testing

It is known that discriminative functions for processing language and spatial data are asymmetrically represented in the human brain (Sperry 1968; Galin 1974; Hécaen 1980). Kinsbourne (1972) originally used lateral eye movements (LEMs) as an indicator of contralateral hemisphere activation to demonstrate that verbal tasks preferentially activate the left cerebral hemisphere and spatial tasks the right. Schwartz et al (1975) performed experiments on 24 healthy students, measuring LEMs, and showed that right-handed subjects tended to look to the left when answering affective questions, supporting the hypothesis that the right hemisphere has a special role in emotion in the intact brain. Ahern and Schwartz (1979) investigated LEMs further using questions to manipulate the affective tone. Their results indicated that negative emotions such as fear are expressed by the right hemisphere, while positive emotions such as happiness and excitement are expressed by the left/dominant hemisphere.

Terzian and Ceccotto (1959) and Terzian (1965) have shown that intra-carotid sodium amytal administered to the right/non-dominant hemisphere produces a "euphoric" reaction, while a "depressive-catastrophic" reaction occurs with a left/dominant intra-carotid sodium amytal infusion. Perria et al (1961) also injected amobarbital into the carotid arteries of patients, and found the occurrence of speech disturbances with a depressive type reaction when the drug acted on the dominant hemisphere, and the absence of speech defects with a euphoric emotional reaction on the non-dominant side.

Dimond and Farrington (1977) used a contact lens method which directed visual input to either the left or right cerebral hemisphere, and showed films to each hemisphere in turn, while the heart rate was recorded. The right hemisphere showed enhanced response to a film of a surgical operation, whilst the left hemisphere responded most to a cartoon. It was concluded that the right hemisphere acts as the dominant trigger to unpleasant emotional experience, and that probably a division of labour for the production of different types of emotion exists between the 2 hemispheres.

Moreover, the existence of lateralised asymmetries in neurotransmitter systems have been reported recently (Nieoullon et al 1977; Oke et al 1978).

4.2.ii. Clinical studies on neuropsychiatric patients

4.2.ii.a. Head injury patients

Hillbom (1960) investigated 359 cases of head injury and found that there were significantly more left-sided injuries associated with psychiatric disturbance. In addition, he found 63% of the psychoses were associated with left-sided lesions, as compared with 26% right-sided and 11% bilateral. Lishman (1968) also studied patients with focal brain damage, and showed an association between affective disorders and damage to the non-dominant cerebral hemisphere. In addition, psychiatric morbidity was associated with temporal lobe wounds especially of the left hand side.

Studying patients with damage to the right side of the brain, Gainotti (1972) has shown their tendency to disinhibition, indifference and joking, suggesting again that the non-dominant hemisphere may have a particular role in mediating emotional behaviour.

Wechsler (1973) demonstrated a relationship between affective memory processes and laterality of cerebral lesions: recall of emotionally charged stories was more impaired in right than in left brain damaged patients, whereas recall of neutral narrative texts was not.

4.2.ii.b. Schizophrenia

Several studies provide evidence of left hemisphere or bilateral hemisphere dysfunction in patients with schizophrenia. Gur (1978) using LEMs found that schizophrenic patients had evidence of left hemispheric dysfunction, when compared to healthy controls. LEMs refer to the shifts in gaze to the right or left that occur when people engage in reflective thinking (Ehrlichman and Weinberger 1978). Schweitzer et al (1978) working on the premise that initial LEMs have been shown to be associated with activation of the contralateral frontal lobes, used LEMs as a marker of activation, and compared schizophrenics to normals with respect to processing various types of stimuli. Results indicated that schizophrenics initiated thought in their left hemisphere significantly more than controls, and reacted with inappropriate initiation of thought in the left hemisphere: both findings were felt to indicate left hemisphere disorder.

Roemer et al (1978) measured visual evoked potentials (VEPs) in schizophrenic patients and compared them to other categories of patients and normal controls. Results showed that low VEP wave form stability, found generally in schizophrenics, was significantly lower on the left than the right side. Buchsbaum et al (1979) also demonstrated hemispheric differences using VEPs in schizophrenics, which were suggestive of a left hemisphere abnormality.

Other support for left hemispheric dysfunction in schizophrenia has been that of Gruzelier and Venables (1973) who demonstrated abnormal lateralisation of skin conductance in their patients.

Others (Quinan 1930; Gur 1977) have reported a high incidence of sinistrality in schizophrenics, again possibly suggesting left hemisphere dysfunction in some of these patients. Lishman and McMeekan (1976) reported increased mixed and left handedness in psychiatric patients, especially the psychotics, including both schizophrenics and manic-depressives, who were mainly males.

Serafetinides (1973) reported that in some schizophrenic patients treated with chlorpromazine, there is an increase in EEG amplitude over the left hemisphere. Other EEG studies (Abrams and Taylor 1979; 1980), showed abnormal EEGs in schizophrenics lateralised to the left hemisphere. Moreover, analysis of the specific cortical area involved showed that the left temporal lobe was affected, and, in the latter study, the abnormality was significantly correlated with formal thought disorder and emotional blunting, but not with first rank symptoms.

Bazhin et al (1975) carried out an investigation using 30 paranoid schizophrenics who experienced auditory hallucinations, and compared them with 12 paranoid schizophrenics without auditory hallucinations, and 10 healthy individuals, all with normal hearing. Using the thresholds of tone signals of different duration, the author's figures showed that the results of testing the paranoid schizophrenics without auditory hallucinations and normal controls showed no difference; however, in the schizophrenic patients who had auditory hallucinations the findings were indicative of left temporal lobe pathology. Dichotic listening studies have shown that there was poorer recall on drug (chlorpromazine) when right ear digits were louder than left ear digits, which would be consistent with the phenothiazines acting to facilitate an over-activation of the left hemisphere in schizophrenia (Gruzelier and Hammond 1980).

Neuropsychological testing of patients with schizophrenia, affective illness and controls have produced fairly consistent findings. Results of an aphasia screening test (Taylor et al 1979) indicated that schizophrenic patients made more total errors and more dominant temporal/ temporo-parietal errors than patients with affective disorders. Abrams et al (1981) demonstrated that an individual WAIS* subscale analysis showed that, compared with patients with affective disorder, schizophrenics had relatively poorer performance on language than non-verbal tasks, indicating dominant hemisphere dysfunction is greater in the schizophrenic group. Using a standardised neuropsychological test battery to study cortical function in 17 patients with schizophrenia and 52 with affective disorders, Taylor et al (1981) found that on tests of dominant hemisphere function, schizophrenics performed significantly worse than those with affective disorders. On tests of non-dominant function, their performances were essentially similar.

There are, however, some studies which do not confirm the data provided so far. EEG investigations showed abnormal activity of the right side of the brain in children at high risk for schizophrenia and schizophrenics, especially in temporo-parietal leads (Itil et al 1974; Giannitrapani and Kayton 1974). Beaumont and Dimond (1973) found decreased left hemisphere performance on a letter matching task in schizophrenic subjects when compared to normal controls, and decreased right hemisphere performance for digit matching when compared to psychiatric controls: the authors felt that the most direct explanation of their results, is that in schizophrenia the 2 cerebral hemispheres are partially disconnected, and that this reflects some change in the efficiency of the corpus callosum.

*Wechsler Adult Intelligence Scale

4.2.ii.c. Depression

Several studies have offered evidence of right hemisphere dysfunction in depression. Gruzelier and Venables (1974) reported that skin conductance response was relatively higher in the left hand in depressive patients than in normal subjects. Myslobodsky and Horesh (1978) also found that electrodermal activity was higher on the left than on the right in endogenously depressed patients, and left sided activity was found to be elevated in endogenously depressed patients compared with controls. They offered evidence that electrodermal activity reflects contralateral rather than ipsilateral hemispheric activity and so concluded that right hemispheric dysfunction was characteristic of depression. Buchsbaum et al (1979) using evoked potentials reported abnormalities of the right side in patients with affective illness.

Folstein et al (1977) compared 10 patients with right and 10 patients with left cerebrovascular accidents, and found a syndrome of irritability, loss of interest and depressed mood in 70% of the right brain stroke group, compared with 0% of the left brain stroke group and orthopaedic control patients: Hamilton Depression Rating Scale Scores were highest in the right stroke group, as were total PSE scores of psychopathology. Kronfol et al (1978) treated 9 depressed patients with unilateral dominant ECT and 9 matched depressed patients with unilateral non-dominant ECT. Bilateral seizures were induced. Neuropsychological tests showed that before treatment, the right hemisphere functions were more abnormal than the left; after ECT, whether left or right sided, when the depression improved, the right hemisphere functions were also improved.

In contrast, d' Elia and Perris (1973; 1974) reported left hemisphere dysfunction in depressed patients. They found that in depressed patients EEG amplitude variability and average evoked response amplitude before treatment were significantly less over the left hemisphere than over the right. After treatment both measures increased over the left to equal or surpass values over the right.

For years now bilateral ECT has been compared with unilateral ECT applied to both dominant and to the non-dominant hemisphere. These studies help provide further knowledge on the neurophysiological organisation of mood. d' Elia (1970) and Sand Strömgren (1973) verified that the depression-relieving effect of bilateral and unilateral non-dominant ECT was equivalent. Reviewing 29 studies with adequate methodology carried out between 1964 and

1973, thus cumulating 619 depressed patients given bilateral, and 720 given unilateral non-dominant ECT, d' Elia and Raotma (1975) confirmed that the therapeutic efficacy was similar, and the average number of treatments equal. It is also known that, quite apart from the verbal-dysmnesic consequences, dominant ECT is less effective than bilateral ECT (Halliday et al 1968; Cronin et al 1970; Cohen et al 1974). In addition, some investigations have found non-dominant ECT to be equal or superior to bilateral ECT in antidepressant efficacy (Martin et al 1965a; Halliday et al 1968; Valentine et al 1968; Zinkin and Birtchnell 1968; Cohen et al 1974). These results reflect the importance of the non-dominant hemisphere in the organisation of mood, and consequently being affected in depressive illness.

Hommes and Panhuysen (1974) reported a study of lateralised hemispheral lesions and found that lesions of the dominant hemisphere are associated with a type of depression, while lesions of the non-dominant hemisphere with a type of euphoria.

On the other hand, Blanc (1962), in a review and reporting his own work, made the point that in neurologically normal psychiatric patients, left temporal foci are frequently seen. Moreover, in a group of 50 patients with various neuroses who developed depressive illnesses, substantially more left temporal foci were found than in normals or psychiatrically ill patients.

In summary, many authors seem to agree that the non-dominant hemisphere may be involved in the organisation of mood, and be particularly implicated in the pathophysiology of depression: however more work is needed to substantiate these claims.

4.2.ii.d. Epilepsy

There is a growing literature on the behavioural correlates of laterality of lesions in the field of epilepsy.

Aggression

Several studies report a positive association between aggression, psychopathy, and/or behaviour disturbances in people with epilepsy with a left sided temporal focus (Hughes et al 1961; Serafetinides 1965; Taylor 1972; Blumer et al 1974; Bear and Fedio 1977; Stores 1977). Moreover, 2 of the studies

indicate that young boys are particularly at risk. Only the investigation of McIntyre et al (1976) reported 11 out of 22 young adults with right sided temporal lobe foci to be significantly more impulsive and aggressive than those with left sided lesions. Mignone et al (1970) suggested that a greater proportion of aggressive psychomotor epileptics had bilateral foci than did non-aggressive patients. These findings must be interpreted with caution, in view of the Kligman and Goldberg (1975) review, mentioned earlier.

Prognosis studies

Lindsay et al (1979a) reported on the long term 16 year follow up embracing social outcome and childhood factors among a group of 100 children with TLE. There were 25 children in the sample for whom bilateral foci were recorded. The remaining 75 had a clear right or left focus. Only 12% of those with a left sided focus were able to achieve "Group A" status, which involved being able to support themselves socially and economically, seizure-free, and not receiving anticonvulsant medication. On the other hand, 43% of the patients with a right sided focus were classed as "Group A".

Psychosis, neurosis and affective disorders

Flor-Henry (1969) set the stage for investigating the laterality of a focus in epileptics with psychoses and the affective disorders, when he reported on a retrospective study of 50 cases of TLE who had, at any time, also been classified as psychotics, and comparing them with 50 non-psychotic TLE patients. He concluded that patients with a schizophreniform psychosis were liable to have epilepsy lateralised to, or involving the left/dominant hemisphere, while the highest incidence of right/non-dominant foci was found in those with manic depressive psychoses. Table 20 shows studies suggesting a left sided temporal lobe focus associated with the phenomenology of schizophrenia or a schizophreniform psychosis. Several studies (Flor-Henry 1969; Lindsay et al 1979b) also show psychosis associated with bilateral lesions, but in very few cases did a schizophreniform psychosis occur with a right sided lesion (Taylor 1975), except when a patient was left handed (Trimble and Perez 1983 - personal communication). There are, however, several studies which have come up with negative results in this regard, in particular those of Mignone et al (1970), Jensen and Larsen (1979b) and Shukla and Katiyar (1980). The point has been made, that none of these latter authors examined in detail the phenomenology, using only clinical criteria for assessment: the authors that have demonstrated a laterality

effect have tended to be predominantly British, whose diagnostic criteria for the assessment of schizophreniform psychosis have been based on Schneiderian principles (Trimble and Perez 1982).

TABLE 20: STUDIES IN PATIENTS WITH TEMPORAL LOBE EPILEPSY SHOWING A LEFT SIDED FOCUS ASSOCIATED WITH A SCHIZOPHRENIFORM PSYCHOSIS

Author	Year	Number Of Psychotic Patients	Number With Left Focus	Number With Right Focus	Bilateral	Controls
Flor-Henry	1969	21	9	2	10	+
Gregoriadis et al	1971	43	43	0	0	-
Taylor	1975	13	9	4	0	-
Hara et al	1980	10	6	4	0	-
Toone and Driver	1980	12	4	0	8 (6L>R)	+
Ounsted and Lindsay	1981	9	7	0	2	-
Sherwin	1981	6	5	1	0	-
Sherwin	1982	7	5	2	0	-
Trimble and Perez*	1983	11	8	2	1	+
TOTAL		132	96	15	21	

> = More than

* = Personal Communication

Note: The 2 reports by Sherwin are of different studies

Flor-Henry (1969) first put forward the suggestion that there is an association between non-dominant or right sided temporal lobe lesions and manic-depressive illness; there were, however, only 9 patients in the group. It is perhaps not surprising that later support for this has not been vast (Gregoriadis et al 1971; Sigal 1976; Taylor 1975; Hara et al 1980). Dalby (1971) found an accumulation of right sided temporal spike foci in his group of 54 psychiatrically abnormal psychomotor epileptic patients. Fifteen of 19 patients with a right temporal spike focus were in this group, while only 5 of 18 patients with a left focus were found in the psychiatric group. This accumulation of right sided spike foci was evenly distributed in the subgroup of "non-phasic abnormalities" (depressive neurotics, patients who had "affective over reaction" to trivial situations, and other neurotics) and "phasic abnormalities" (18 endogenous depressives, 2 manics and 2 schizophreniform psychoses). This would broadly agree with the findings of Flor-Henry (1969).

Bear and Fedio (1977) demonstrated that, in the absence of psychosis, the personality characteristics of right and left temporal lobe epileptics differed: the right temporals were more depressed and emotionally labile.

Taylor (1972) found neurotic syndromes to be related to a non-dominant temporal lobe lesion. Shukla and Katiyar (1980) analysed the relationship between psychiatric diagnosis and the side of the temporal EEG focus in 62 patients with TLE: the only significant findings were that neurotics had right temporal foci.

Wolf (1982) reported manic syndromes in 6 patients, one with generalised epilepsy and 5 with TLE: all the latter but one had a left sided EEG focus.

Weil (1956) described in detail 2 out of 7 patients with ictal depression: one had left temporal lobe damage, but bilateral EEG abnormalities, while the other had right temporal lobe abnormalities.

Miscellaneous neuropsychiatric disturbances

Bear and Fedio (1977) administered an 18 item trait questionnaire to 48 TLE subjects, 27 of whom had unilateral foci. Statistical significance was achieved on various items. Right TLE patients described more elation, emotionality, sadness, viscosity and obsessionalism; left TLE subjects described more anger, paranoia and dependence. Roberts et al (1982) suggested that hypergraphia, elation, hyperreligiosity and déjà vu

experiences occur more frequently in patients with right sided, non-dominant temporal lobe lesions.

4.3. Discussion and Conclusions

Before arriving at any conclusions, it would be worthwhile to look at some of the pitfalls of the studies. A criticism which may be lodged at many of the works is the question of handedness and cerebral dominance. This may even be directed at Flor-Henry (1969) who assumed that only 5% of his sample of epileptics were left handed, which is roughly the prevalence in the general population (Bingley 1958; Toone and Driver 1980). However, in people with epilepsy, a raised incidence of left handedness has long been reported (Bingley 1958). Later studies have confirmed this, and sinistrality has been found to occur in roughly 17% of epileptics (van der Vlugt and Bakker 1980), especially those with psychosis (Toone and Driver 1980). Left handed patients should be discounted from any series, as the conventional tests for dominance such as LEMs (Ahern and Schwartz 1979), writing posture (Levy and Reid 1976), and dichotic listening (Kimura 1967; Geffen et al 1978), have been challenged by several workers (Pratt et al 1971; Gur et al 1975; Ehrlichman and Weinberger 1978; Warrington and Pratt 1981).

Warrington and Pratt (1981) suggest the only certain way to determine the dominant hemisphere for language in left handed patients is by comparing the effects of unilateral ECT to the right and left hemisphere; transient dysphasia occurs after ECT to the language dominant hemisphere. Another method for assessing language dominance with reported 95% accuracy is the occurrence of dysphasia after unilateral injection of sodium amylobarbitone into the carotid artery (Wada and Rasmussen 1960; Perria et al 1961; Branch et al 1964). However, ethical problems may well arise if ECT or intra-carotid infusion were used as methods of assessing laterality for research purposes.

Branch et al (1964) estimate that 90% of normal right handers and 64% of normal left handers or ambidextrous people have speech functions represented in the left hemisphere. Ambidextrous patients should therefore also be discounted from studies on laterality.

Moreover, the lateralisation of a focus by EEG is by no means conclusive. Wieser et al (1979) presented data on 133 patients with uncontrolled temporal lobe seizures who underwent bilateral stereoelectroencephalographic exploration, and found that only two thirds of all seizures which are spontaneous or induced, were in accordance with the paroxysmal interictal activity with regard to side of origin. That is, one third of the seizures give results which conflict with the information provided by interictal activity.

Other problems encountered are the small numbers of patients which were investigated in most studies, patient selection (a relatively high proportion of the epileptics in psychiatric clinics have temporal lobe pathology), and lack of uniform diagnostic criteria.

In summary, taking all the evidence into account, it seems fair to conclude that left sided cerebral damage predisposes to psychiatric disability and this is possibly more so when the damage involves the temporal lobe. In children this may be shown by aggression and behaviour disturbances. It renders the adult more liable to psychosis. When the psychosis is schizophreniform, phenomenologically speaking, the damage is more likely to be in the left temporal lobe. This may implicate especially those with auditory hallucinations. One may be tempted to say that disturbances such as neuroticism and affective changes are more likely to be associated with the right side, but further research should be done before this can be said with any confidence.

In conclusion, Gruzelier (1981) reviewed the subject of laterality and deduced that the neuropsychology of psychopathological states is in its infancy; simple notions have given way to more complex models: "the likelihood of hemispheric asymmetries in the neurotransmitter systems, and the evidence of alterations in lateralised processes on neuroleptics, may elucidate the therapeutic actions of drugs in psychiatric practice".

SECTION II

THE INVESTIGATION

CHAPTER 5

MATERIALS AND METHODS

5.1. The Phenomenology of Depression in People with Epilepsy

5.1.i. Subjects

Eighty consecutive referrals over a 2 year period, to the Department of Psychiatry at the National Hospital for Nervous Diseases, Queen Square, (NHQS) London, and the Chalfont Centre for Epilepsy, Buckinghamshire, with a clinical diagnosis of both epilepsy and depression, were screened by the investigator for possible inclusion in the study.

General criteria for admission to the project were:-

1) Aged between 18 and 70 years
2) English speaking
3) No evidence of mental retardation
4) No significant medical or surgical illness

In addition, patients with an estabilshed diagnosis of epilepsy and fulfilling the following criteria (Pond et al 1960; Hopkins and Scambler 1977) were included:-

1) Patients who had more than one non-febrile seizure of any type.
2) Patients must have had at least one seizure in the preceding 2 years, and/or were on continuing anticonvulsants for more than one non-febrile seizure in the past. Moreover, all of the patients were either referred by, or being followed up by, consultant neurologists at the NHQS or the Chalfont Centre, and, if there was any doubt as to the diagnosis of epilepsy, the patient was excluded.

In addition, the patients had to be diagnosed as depressed and fulfil the Research Diagnostic Criteria for major depressive disorder (Spitzer et al 1978) (see Appendix 1), and score over 12 on the Hamilton Depression Scale (Hamilton 1967).

Patients who were pregnant, or who had a history of alcohol or drug abuse were excluded.

5.1.ii. Types of data collected

5.1.ii.a. Clinico-social data

The patients included in the study were interviewed by the investigator for details of their own past psychiatric history, as well as details of a family history of epilepsy, depression, suicide, alcoholism, psychosis or other psychiatric illness.

The patients were questioned as to their seizure frequency prior to the onset of the depression, and were classified into 3 categories: those with a normal/usual seizure frequency, and those with increased or decreased seizure frequencies. Where possible, additional information was obtained from hospital case notes.

Hand preference was assessed by means of the Annett hand preference questionnaire (Annett 1970) (see Appendix 2). Annett (1970) reports finding 23 subgroups of handedness, but a reduction of these to 6 groups (Taylor et al 1982) makes a study much more realistic and manageable. If the "either" responses are disregarded (as suggested by Annett 1983 - personal communication), then only 3 groups remain, namely: dextrals, sinistrals and mixed handers. This is what was done in the present study.

The epilepsy diagnoses of all patients were made by Dr. M. Trimble, Consultant Psychiatrist, blind to the EEG assessments and details of the patients' depression.

5.1.ii.b. Special investigations

Blood samples were analysed for red blood cell (rbc) and serum FA, by the Department of Haematology, NHQS. As a control, assays were performed for rbc and serum FA on 180 consecutive blood samples sent for routine haematological investigations, to establish a range of values and a mean, at the time of the present investigation, to obviate any experimental bias. The rbc and serum FA were determined using the Amersham International Vitamin B12/Folate Dual Radioassay Kit. The values for rbc and serum FA using the Kit are suggested as follows:

Serum FA:	Low	<2.0ng/ml
	Intermediate	2.0 to 2.5ng/ml
	Normal	>2.5ng/ml
Rbc FA:	Normal	160 to 640ng/ml

Reynolds et al (1970) regard serum FA levels of less than 2.5ng/ml as subnormal.

The patients were referred for psychometric testing to the Departments of Neuropsychology at the National Hospitals, where they were assessed using the Wechsler Adult Intelligence Scale (WAIS).

Electroencephalograms were performed in the Department of Clinical Neurophysiology. All patients had at least one EEG, although most had several. All EEGs were classified by Dr. HRA Townsend, Senior Consultant in Clinical Neurophysiology. He assessed the EEGs blind to all clinical details of the patients. As a control group, the EEGs of 66 age and sex matched consecutive patients with a diagnosis of epilepsy, and who were not psychiatrically impaired, were assessed. The EEGs were classed as follows: (1) normal (2) generalised diffuse (generalised spike and wave activity) (3) left temporal (4) right temporal (5) bilateral temporal (6) other focal (when spike and wave activity was clearly localised) (7) non-specific abnormality (abnormal generalised activity but with no spikes and waves) and (8) other (any abnormality not accounted for in the previous categories).

Patients also had computerised axial tomography (CAT) Scans to detect any localising or lateralising abnormalities.

5.1.ii.c. Psychological data

The Research Diagnostic Criteria were used as a requirement for the diagnosis of depression to permit entry of a patient to the study. Rating scales were employed to measure the severity and type of depression, the presence and severity of anxiety, the severity and direction of hostility, the amount of neuroticism and extraversion, and the presence of obsessoid or hysteroid traits. The rating scales employed are shown in Table 21, and a detailed description of them will follow.

TABLE 21: RATING SCALES USED

Parameter Measured	Rating Scales	Rater
Type of Depression	i Newcastle Diagnostic Scale	Physician
	ii Levine-Pilowsky Depression Questionnaire	Patient
Severity of Depression	i Hamilton Depression Scale	Physician
	ii Beck Depression Inventory	Patient
	iii Levine-Pilowsky Depression Questionnaire	Patient
Anxiety	State-Trait Anxiety Inventory	Patient
Hostility	Hostility and Direction of Hostility Questionnaire	Patient
Neuroticism Extraversion	Eysenck Personality Inventory	Patient
Hysteroid and Obsessoid Traits	Hysteroid/Obsessoid Questionnaire	Patient

The Research Diagnostic Criteria (RDC)

The RDC (see Appendix 1) were developed in 1975 to enable research investigators to use consistent sets of criteria for the description and selection of samples of subjects with functional mental disorders (Spitzer et al 1978). The RDC were an expansion and elaboration of some of the criteria developed by the St. Louis group, often referred to as the "Feighner criteria" (Feighner et al 1972). Since its initial publication, the RDC has incorporated minor modifications resulting in the current third edition, the one used in the present investigation.

During the last few years, large numbers of investigators throughout the world have used the RDC in their research studies, resulting in much greater specificity in defining and describing samples of subjects than had been achieved previously (Williams and Spitzer 1982). The criteria have been shown to be reliable (Spitzer et al 1978), and for this reason, amongst others, they were used as the basis for the major diagnostic categories of the third edition of the American Psychiatric Association's Diagnostic and

Statistical Manual of Mental Disorders (DSM III) (Williams and Spitzer 1982). The symptomatic inclusion criteria for major depressive disorder (RDC) and major depression (DSM III) are almost identical; however, the RDC excludes the presence of certain Schneiderian first-rank symptoms and evidence of formal thought disorder, when accompanied by certain other symptoms such as blunted affect. This is only one of several differences between the RDC and the DSM III.

The RDC permits subclassification of affective disorders into overlapping categories, but this was not done in the present study.

The Hamilton Depression Rating Scale (HDRS)

The original version (Hamilton 1960) was revised in 1967 (Hamilton 1967) (see Appendix 3). The HDRS was designed for use to measure the severity of the depression in patients already diagnosed as suffering from depressive illness. It is an observer rating scale intending to assess the present state of the patient's condition and over the preceding few days. No distinction is made between intensity and frequency ratings. It reflects what would happen in an ordinary clinical interview: it is nothing more, in fact, than a well standardised structured interview. The items on the HDRS are rated according to severity either on a 0 - 2 point or a 0 - 4 point scale, and the rating by the clinician is completed as a result of a clinical interview, and it takes into account information concerning the patients' behaviour during the preceding week. The HDRS is both valid and reliable (as will be discussed later) and for these reasons it has become accepted internationally as a measure to be used in psychiatric research.

The standard HDRS consists of 17 items and the range of scores is from 0 to 52. However, in the present investigation it was decided to employ the 3 additional items, as the aspects they describe, namely paranoia, obsessionalism and depersonalisation have been noted to occur fairly frequently in people with epilepsy, as was reported in the introductory chapter. The items were included to discover whether they were present, or more florid in form when a patient with epilepsy became depressed, and whether they are helped by treatment of the depression. The fourth item of the 21 item HDRS (diurnal variation in mood) was included for the sake of completeness. The total scores in this version range from 0 to 64. In order to obviate the possible bias of the rater, it was decided to assess the reliability between 2 raters of the same interview. This was done on a smaller group of 13 patients at the start of the investigation. The inter-rater reliability was found to be high ($r = .94$; $p < .001$, Pearson correlation coefficient: $r_s = .92$; $p < .001$, Spearman correlation coefficient).

Moreover, in the therapeutic trial, the rater was blind to what therapy had been used and therefore was not influenced by a personal preference for any given treatment. The HDRS is weighted toward somatic symptoms and behavioural features of depression, whereas the Beck Depression Inventory is concerned more with the psychological and cognitive features, embracing pessimistic thoughts, failure and self-punitive wishes; the scales are therefore somewhat complementary.

Various cut-off points for the HDRS have become standard for determining levels of severity, as follows: a total score greater than 24 (or 25) for severe depression (inpatients), greater than 17 for mild depression (outpatients), and less than 6 for essentially no depression (Endicott et al 1981). Dewan et al (1982) recommend 17 as the cut-off score on the 21 item Hamilton for outpatient research on depression, and they feel that a higher score indicates significant depression.

The HDRS was chosen in this study for several reasons. Firstly, it is the most widely used physician rating scale for the measurement of the severity of depression. The importance of a physician rating scale is that the doctor can observe and assess certain manifestations of a depressive illness which a patient would be unable to do, such as the evaluation of insight, hypochondriasis, retardation or agitation, and presence of delusions, all of which are included on the HDRS. Furthermore, a skilled observer, by reason of his training or experience, has standards against which he can evaluate the intensity of any one symptom, whereas a patient has no such standards: "severe", "moderate" and "mild" have no meaning to a patient, except in relation to his or her own experience. Secondly, although the HDRS was designed for use with patients already diagnosed as suffering from depressive illness, it has also been found useful with general medical patients (Schwab et al 1967b), patients with Parkinsonism (Coppen et al 1972c; Robins 1976) and patients with epilepsy (Roy 1979). Thirdly, it can be used as a measurement of improvement in the patients' depression (Le Gassicke et al 1964; Rose et al 1965; Waldron and Bates 1965; Sheehan 1981). Fourthly, the last 3 items, namely depersonalisation and derealisation, paranoid symptoms and obsessional symptoms are of particular interest in patients with epilepsy.

In addition, the HDRS is both valid and reliable. Its validity was demonstrated by Schwab et al (1967a) who found it discriminated between medical and depressed patients. Another way of assessing validity is to compare the scores on different scales. Several have found the HDRS to correlate well with global severity ratings, using other rating scales or

clinicians' judgement (Bech et al 1975; Knesevich et al 1977; Montgomery and Åsberg 1979). Others obtained good correlations between the HDRS and the Zung Depression Scale (Zung 1969; Brown and Zung 1972; Carroll et al 1973b). Zealley and Aitken (1969) demonstrated a high correlation between the HDRS and the Visual Analogue Scale. The HDRS is reliable, and several papers have reported a high inter-rater reliability of the HDRS (Waldron and Bates 1965; Bech et al 1975; Hamilton 1976; Bech et al 1979).

The Beck Depression Inventory (BDI)

One of the first self-rating scales for depressive symptomatology was the BDI (Beck et al 1961), (see Appendix 4). It contains 21 groups of items and each group consists of a graded series of 4 to 6 statements. The patient is asked to select a single statement in each group that corresponds most closely with his actual condition at that particular time.

Each category describes a specific manifestation of depression. The statements are ranked to reflect the range of severity of the symptoms from neutral to maximal severity. Numerical values from 0 - 3 are assigned to each statement to indicate the degree of severity. In many groups, 2 alternative statements are presented at a given level and are assigned the same weight, as can be seen with the first group. The items do not reflect any theory regarding the aetiology or underlying psychological processes in depression.

The total BDI score is obtained by adding the scores of the items and the range is 0 to 62. Beck (1967) suggests a score of 13 as the cut-off point between depressed and non-depressed patients. More recently, Beck and colleagues (Kovacs et al 1981) suggested a BDI score of 10 be considered as the cut-off point, and patients scoring 9 or under be considered as not depressed.

Although originating in the USA, the BDI has been validated on English patients (Metcalfe and Goldman 1965), and a cut-off point of 11 has been suggested for British subjects (Metcalfe and Goldman 1965; Salkind 1969).

The BDI was chosen for several reasons. It has been used to measure the presence and severity of depression in medical inpatients, including 19 neurological patients (Schwab et al 1967a), patients with Parkinsonism (Coppen et al 1972c) and subjects with physical complaints (Armstrong et al 1980). Salkind (1969) has found the BDI useful in general practice. In

clinical research, measurement of change in a depressive mood is an important factor. Two studies were concerned with the evalution of this, and concluded that the BDI is sensitive to improvements in symptomatology (Little and McPhail 1973; Johnson and Heather 1974).

In its favour, it is a simple scale for the patient to complete and it has a high reliability; the split half reliability is .86, and a figure of .93 for a scale of full size (Hamilton 1969). It has been shown by Beck to have a high validity when compared against overall ratings, but it must be remembered that the original series on which validity was tested contained 28% of patients who were schizophrenic (Hamilton 1969).

Comparison between the Beck Depression Inventory and the Hamilton Depression Rating Scale

Comparisons between the 2 scales have shown them to be highly correlated yet complementary. Schwab et al (1967a) compared the HDRS and BDI on 153 medical in-patients who were evaluated for depression. Using the Spearman Rank Correlation Coefficient to compare the patients' total scores on the 2 scales, a high correlation (r_s = .75) was obtained. Burrows et al (1972) studied 32 depressed in-patients rated by the HDRS and BDI during an antidepressant drug study. Before treatment the HDRS-BDI correlation (calculated from the published raw data) was τ = .41; p = .002), using the Kendall correlation coefficient.

Nielsen et al (1972) conducted a study of 500 general medical out-patients, from whom they selected a smaller group of 50 after applying a cut-off criterion of 13 on the BDI results. These patients were then evaluated by interview and with the HDRS, and the correlation which emerged between the HDRS and the BDI was .54. As in the previous study of Schwab et al (1967a), however, not all of these patients could reasonably be said to suffer from a primary depressive illness, as they had medical illnesses. Williams et al (1972) administered the HDRS and BDI to 10 severely depressed patients and demonstrated a statistically significant correlation between the 2 scales (r = .82; $p < .05$). Bech et al (1975) assessed 24 depressed patients using both scales, and demonstrated a high degree of correlation between the scores (r_s = .72; $p < .001$).

Bailey and Coppen (1976) compared the 2 scales in the assessment of 42 in-patients suffering from a depressive illness. They were assessed on admission and then over a period of some weeks during which the majority were successfully treated and improved. Satisfactory and significant correlations were observed in two thirds of the patients, the overall correlation covering the 425 pairs of scores being statistically significant ($r = .68$; $p < .001$). In the remaining third, however, the results were often found to be divergent. There were no obvious characteristics of the latter group that distinguished them either in personality or in severity of illness. The authors concluded by remarking that there was no absolute measure of severity of depressive illness and that, as there are factors such as have been mentioned already which could invalidate either clinical interview or self rating, "in most studies it would be useful to have both forms of measurement". Carroll et al (1981b) confirmed the findings of the earlier workers, demonstrating a statistically significant correlation between the HDRS and BDI scores. All the aforementioned reports compared the 17 item HDRS and BDI.

Sheehan (1981) used the 21 item HDRS and the BDI on 16 depressed patients to assess the severity of depression and response to treatment. Correlations of the 2 scales were as follows:-

Before treatment: BDI and HDRS ($r = .71$, $p < .01$)
After treatment: BDI and HDRS ($r = .68$, $p < .01$)

Georgotas et al (1982) also used the 21 item HDRS, BDI and Clinical Global Impression Scale (CGI) on 60 patients in a 4 week antidepressant trial. The HDRS and CGI showed similar results, but there was no significant correlation between the HDRS and BDI scores. It was noted that the scores on the BDI tended to be much more variable than the other outcome measures.

In summary, all workers, except Georgotas et al (1982), found statistically significant correlations between the HDRS and the BDI. The differences in the correlations could be attributed to many factors, namely patient selection, differing expertise in administering the HDRS, and statistical methods used, not all of which were reported.

The Levine-Pilowsky Depression Questionnaire (LPD)

The LPD (Pilowsky et al 1969), (see Appendix 5), originated as a self-rating questionnaire designed to identify and classify subjects complaining of depression into groups. A number of statements relating to endogenous and neurotic depressions were collated from standard psychiatric texts, and from them, a 57 item questionnaire requiring yes/no answers was constructed. The LPD contains items related to somatic aspects of depression (sleep, appetite, weight, libido), aetiological factors (life events), behavioural aspects (daily activities and coping abilities) as well as the psychological and cognitive concomitants (feelings of gloom, worthlessness, depression, pessimism and cognitive abilities). On the basis of responses to the questionnaire, patients are classified into one of 3 classes.

The first class represents a mixed group of depressive reactions, which is common to a wide spectrum of psychiatric patients, regardless of diagnosis. In other words, there are a number of patients, part of whose illness could be described as a reactive depression; this group is regarded to represent non-endogenous depressives. The second class includes those patients with an endogenous depression with the classical symptoms being retardation, loss of interest in life, visceral symptoms, lack of precipitating stress, middle insomnia, suicidal ideation and guilt. The third class is considered non-depressive.

The questionnaire was validated by studies showing that the more endogenously depressed patients were more often treated with ECT, and, as expected, showed a good response to such treatment (Pilowsky and Boulton 1970; Pilowsky and McGrath 1970).

Pilowsky and Spalding (1972) derived a depression scale from the original questionnaire with depression scores ranging from 1 to 20. Investigators have found highly significant correlations between the LPD Depression score and the Zung depression scale (Byrne 1975) and the Visual Analogue Scale for depression (Levine 1975).

The questionnaire was chosen as it is the only self-rating scale which classifies depressions into endogenous and non-endogenous. It has, in addition, a score for the measurement of severity. A good feature of the questionnaire is that it has several "correction" questions, which test the responders' comprehension and consistency in answering.

The Newcastle Scale

To complement the self-report LPD scale for measuring endogenicity, it was decided to employ a physician rated scale to assess the same dimension.

The Newcastle scale (Carney, Roth and Garside 1965) contains a diagnostic scale and an ECT prediction scale. The diagnostic scale gives a total score, with a range from -2 to +12. It comprises 8 positively and 2 negatively weighted items, which are summed to give a diagnostic score. The higher scores (6 or more) indicate endogenous depression, while the scores of 5 or less relate to what is generally known as non-endogenous, neurotic or reactive depression. Appendix 6 shows the Newcastle diagnostic scale items, the weighted scores given to each item (based on the factor analysis based on the original 1965 paper), and a list of definitions, most of which come from the original papers, while others come from subsequent papers, (Carney and Sheffield 1972; Schalling et al 1973).

The work of Carney and Sheffield (1972) is a validation of the Newcastle scale, involving both the diagnostic and the ECT prediction scale. The scale has been further validated by its interesting relationship to the results of the DST (Coppen et al 1983; Holden 1983) as discussed earlier. Post (1970) used the diagnostic scale adapted for use with elderly patients, and found it discriminated between deeply melancholic and more neurotic patients. Naylor et al (1971) found the Newcastle diagnostic scale scores to agree both with those of the Kendell scale (1968) and clinical diagnosis in separating psychotic and neurotic illness.

Kragh-Sørensen et al (1973a) demonstrated a high inter-rater reliability using the Newcastle scale.

In the present study, the investigator and a second rater interviewed a group of 13 patients at the start of the investigation, and the inter-rater reliability was found to be high ($r = .89$; $p < .001$, Pearson correlation coefficient: $r_s = .90$; $p < .001$, Spearman correlation coefficient).

The State-Trait Anxiety Inventory (STAI)

The STAI (Spielberger et al 1970), (see appendix 7 a and b), is comprised of 2 separate self-report scales for measuring 2 distinct anxiety concepts: State anxiety (A-State) and Trait anxiety (A-Trait). State anxiety is conceptualised as a transitory emotional state or condition of a person that varies in intensity and fluctuates in time, in reaction to circumstances

that are perceived as threatening. Trait anxiety, on the other hand, is conceived of as a relatively stable permanent personality disposition that tends to remain stable over time and across situations. Theoretically, persons who are high in A-Trait or "anxiety proneness" will exhibit A-State elevations more often, and more intensely than persons low in A-Trait, because they tend to perceive a wider range of situations as threatening (Spielberger et al 1970).

The validity of this concept was investigated by factor analysis (Bartsch and Nesselroade 1973) who obtained results which seemed to support the State-Trait distinction. Clinical investigations (Beutler et al 1977) also suggest that Trait and State anxiety reflect different entities.

The STAI A-State scale consists of 20 statements, that ask people how they feel at the time of filling in the questionnaire. The STAI A-Trait scale also consists of 20 statements that ask people to describe how they generally feel. These scales are printed on opposite sides of a single test form. In the standardisation of the STAI, the A-State scale was given first, followed by the A-Trait scale; and, as this order is recommended when both scales are given together, that is how it was done in the present investigation.

The range of possible scores of the STAI varies from a minimum score of 20 to a maximum score of 80 on both the A-State and A-Trait subscales. Subjects respond to each STAI item by rating themselves on a four-point scale. The 4 categories for the A-State scale are: (1) not at all; (2) somewhat; (3) moderately so; and (4) very much so. The categories for the A-Trait scale are: (1) almost never; (2) sometimes; (3) often; and (4) almost always. Some of the STAI items (eg. "I am tense") are worded in such a way that a rating of "4" indicates a high level of anxiety, while other items (eg. "I feel pleasant") are worded so that a higher rating indicates low anxiety. The STAI A-State scale has 10 directly scored and 10 reversed items. The scores of the directly placed items are weighted as 1, 2, 3, and 4, and for the reversed items are 4, 3, 2 and 1. The STAI A-Trait scale has 7 reversed items, and 13 that are scored directly, with weightings the same as the former scoring pattern (Spielberger et al 1970).

Several studies have demonstrated that State anxiety fluctuates in expected directions dependent on emotional and situational context (Hodges and Spielberger 1969; Johnson et al 1970; Spielberger et al 1970; Wolfer and Davis 1970; Martinez-Urrutia 1975; Kendall et al 1976; Wadsworth et al 1976; Kendall 1978; Teichman 1981), whereas Trait anxiety remains relatively stable over time (Johnson 1968; Johnson and Spielberger 1968; Wadsworth et al 1976; Valle and DeGood 1977; Teichman 1981), and is impervious to stress (Auerbach 1973a; 1973b; Spielberger et al 1973).

The reliability of the STAI A-Trait scale is relatively high, but low for the STAI A-State scale, as would be expected for a measure designed to be influenced by situational factors (Spielberger et al 1970). Evidence of the validity of the STAI A-Trait comes from high correlations (.79, .80, .83) found by Spielberger et al (1970) between the scale and the Taylor Manifest Anxiety Scale (Taylor 1953), which also measures A-Trait anxiety.

The scale was chosen as it measures both State and Trait anxiety, where the former is sensitive to change, and the latter stable and reliable. In addition, it is widely used (Smith and Lay 1974; Howarth and Schockman-Gates 1981) in many parts of the world, including the USA (Spielberger et al 1970; Price and Blackwell 1980), Israel (Teichman 1981), Australia (Astbury 1980) and Britain (Haddad and Morris 1982). Moreover, it has been employed successfully in measuring the 2 types of anxiety in many clinical situations, including various psychiatric illnesses (Spielberger et al 1970), depression (Newmark 1972; Wadsworth et al 1975), migraine patients (Price and Blackwell 1980), surgical patients (Johnson et al 1970; Wolfer and Davis 1970; Auerbach 1973b), methadone addicts before and after their maintenance medication (Teichman 1981) and in pregnancy and labour (Gorsuch and Key 1974; Lederman et al 1978; Beck et al 1980; Haddad and Morris 1982). In addition, the State anxiety has been shown to decrease with treatment for a depressive illness (Newmark 1972).

Normative data (Spielberger et al 1970) give ranges of the mean A-Trait scores from 33 to 38, while the means of A-State range from 35 to 40.

The Hostility and Direction of Hostility Questionnaire (HDHQ)

The HDHQ (Foulds et al 1960; Caine et al 1967), (see Appendix 8), was designed to sample a wide range of possible manifestations of aggression, hostility or punitiveness. The HDHQ is a self-rating questionnaire containing 51 statements which require a true or false answer. The patient fills in the HDHQ by hand and then the researcher checks that all items have been answered. If the respondent fails to record an answer for an item, he/she is urged to say whether the item is "on the whole" true or false. The questionnaire comprises 5 tests, namely:-

1) AH - urge to act out hostility
2) CO - criticism of others
3) PH - projected delusional (ie. paranoid) hostility
4) SC - self criticism
5) G - guilt

The first 3 tests are concerned with extrapunitive areas, while the last 2 cover the intropunitive areas. Hostility is the sum of all 5 tests. Direction of hostility is the sum of the intropunitive tests (with SC counted twice over) less the sum of the extrapunitive tests:-

Hostility = AH + CO + PH + SC + G
Direction of hostility = (2SC + G) - (AH + CO + PH)

The direction of hostility is assumed to approximate to a measure of the direction in which a person turns his hostility, either outwards against other people, or inwards against himself. Extrapunitive scores are designated a minus quantity, while intropunitive scores are given a positive value.

The reliability of hostility by calculation of test-retest correlations was .75 and that of the direction has a reliability of .50; the authors calculated the standard error of measurement for both measures as approximately 3.5 (Caine et al 1967).

Several studies have shown changes in the scores before and after treatment for their psychiatric condition. Neurotics (Caine 1965) and depressives (Foulds 1965; Mayo 1967; Philip 1971; Blackburn 1974; Lyketsos et al 1978) show a drop in hostility and decrease in intropunitiveness with improvement in their psychiatric condition after appropriate treatment.

The Eysenck Personality Inventory (EPI)

A review of the literature by Eysenck (1960) disclosed strong support for a view which recognises the existence of 2 very clearly marked and important personality dimensions; these have been called extraversion-introversion, and neuroticism, emotionality or stability-instability. The EPI (Eysenck and Eysenck 1964), (see Appendix 9), sets out to measure these 2 major dimensions of personality.

The EPI consists of 57 questions requiring a yes-no answer. The items have been carefully worded so that they are understandable by subjects of low intelligence and/or education. The EPI contains a lie scale, (L), which may be used to eliminate subjects showing "desirability response set". The lie scale not only measures dissimulation, but also a stable personality function, the precise nature of which little is known (Eysenck and Eysenck 1975). Of the 57 items, 9 are designated as the L scale, with the remaining 48 being divided equally between the neuroticism (N) and extraversion (E) scores. An L score of 4 or 5 would be considered to constitute the cutting off point where inventory answers cease to be acceptable, and a tendency to have high L scores may in itself be an interesting personality trait (Eysenck and Eysenck 1963). High L scores are usually associated with low N scores and introversion, that is, low on E scores (Eysenck and Eysenck 1963). The mean lie score of a group of 651 subjects was 2.7 with a standard deviation of 1.6 (Eysenck and Eysenck 1964). The mean N value for a normal population is 9.1, while the mean E value is 12.1 (Eysenck and Eysenck 1964).

The EPI was chosen as it has been widely used in various patient populations, but in particular, in patients with depression and others with epilepsy.

Many investigations have confirmed that patients suffering from neurosis have higher N scores than normal people. Knowles (1960) re-tested 40 neurotic patients after one year and found that the average N score of the group was practically unchanged, although the test-retest correlation was not quite so high as that found for normals. Knowles, however did not record whether any important changes in the mental state of the patients had taken place between the 2 occasions. Knowles found little change in the average E score when he retested neurotic patients and the test-retest correlation was as high as that of normal subjects. There seems to be a significant trend for N and E to decline with advancing age; women tend to score higher than men on N and lower on E; as regards social class, there

has been a general tendency for working class groups to be characterised by higher N scores than middle class groups; no differences were observed with respect to E (Eysenck and Eysenck 1964).

Several reports using the Maudsley Personality Inventory (MPI), the forerunner of the EPI, demonstrated that with recovery of depression, N scores fell while E scores rose (Coppen and Metcalfe 1965; Levinson and Meyer 1965; Ingham 1966; Kerr et al 1970). Kendell and Discipio (1968) tested patients with the EPI, while they were depressed, and again after recovery: the mean N score fell, while the mean E score rose.

Knowles and Kreitman (1965) reported their experience using the EPI with neurotic and anxious patients. They found that the E score was stable despite treatment, while the N score fell significantly with treatment. They also found that the L and N scores were significantly and negatively correlated ie. that "normals" are "liars", and "neurotics" are "honest", which is in agreement with studies using the MPI (Gibson 1962; Eysenck and Eysenck 1963). The authors, however, disagreed with a cut-off point of 4 or 5, as they argued that this would thus lead to the exclusion of a substantial proportion of patients. They also argued that Eysenck and Eysenck (1964) demonstrated that conscious dishonesty can influence lie scores (by instructing a group of normal subjects to "fake good"), as "lying" is a complex process and attempts to interpret "lie" scales should be regarded with caution.

More recently Weissman et al (1978) employed the MPI to investigate personality and the prediction of long-term outcome of depression. Results showed that the most important predictor of the clinical outcome was personality as measured by the N scale of the MPI. Hirschfield and Klerman (1979) assessed personality characteristics of depressive and manic patients using a battery of self-report personality inventories including the MPI. Depressive patients demonstrated more neuroticism, introversion and obsessionality than manic patients or normal individuals.

Davies-Eysenck (1950) assessed 38 patients with epilepsy using the MPI. Eighteen of the patients had "grand mal" attacks, 7 "petit mal" and 13 with both types of seizures. The patients scored significantly higher on neuroticism. This did not correlate with the length of time of the epilepsy, which the author felt suggested that the increased neuroticism was "endogenous" and not a reaction to the epilepsy.

Standage and Fenton (1975) examined a series of 37 people with epilepsy using the EPI. Twenty seven were attending a neurological clinic, while the rest were attending a psychiatric clinic. The mean neuroticism score for those attending the neurological clinic was 9.8, while the figure for those from the psychiatric clinic was 12.4. The mean extraversion score for the neurological group was 10.9, with that of the psychiatric group being 11.7.

The Hysteroid/Obsessoid Questionnaire (HOQ)

The HOQ, (see Appendix 10) was devised to measure the hysteroid/obsessoid dimension of personality, which Janet claimed to detect in neurotics and suggested could be considered along a single dimension (Caine and Hawkins 1963). Janet suggested that there are 2 opposing trait constellations, and each may be considered to be compounded from the appropriate terms of the dichotomies shown in Table 22.

TABLE 22: THE ELEVEN SUBSCALES OF THE HOQ

(From Caine and Hope 1967)

Subscale	Hysteroid	Obsessoid	Item Numbers
1	Vivid day dreams	Inability to indulge in fanciful thinking	1 12 25 36 44
2	Enjoys being the centre of attention	Prefers to stay in the background	2 13 21 26 37 46
3	Excessive display of emotions	Scarcely any display of emotions	3 14 22 27 38
4	Given to precipitate action	Slow and undecided owing to weighing of pros and cons	4 15 23 28 39 47
5	Frequent mood changes	Constant in mood	5 16 29
6	Under-conscientious	Over-conscientious	6 17 24 30 40
7	Careless and inaccurate	Stickler for precision	7 18 31 41
8	Over-dependent	Obstinately independent	8 32
9	Desire to impress and gain attention	Self-effacing	9 19 33 42
10	Makes superficial friendships	Makes deep, lasting friendships	10 20 34 43 48
11	Shallow emotionally	Feels things deeply	11 35 45

The HOQ has 48 items, each of which belongs to one of the 11 traits, and no item belongs to more than one trait. The respondent fills in the questionnaire, encircling true or false for each of the 48 items. If the patient hesitates to complete an item, the researcher may urge him/her to say whether it is true or false "on the whole". Patients scoring 24 or more on the HOQ are allotted to the hysteroid category, the rest being regarded as obsessoids, but Caine and Hawkins (1963) make the point that the dividing line is somewhat arbitrary. The HOQ was validated on 93 neurotic patients and found to be reliable using test-retest correlations on 30 normal subjects and 134 psychiatric patients (Caine and Hope 1967). The HOQ and extraversion score of the EPI are to some extent measuring the same dimension, and indeed, in a sample of neurotics the correlation between the HOQ and the MPI "E" scale was high (.70) (Caine and Hope 1964). Hysteroids were significantly more extrapunitive, as measured by the MMPI (Caine and Hawkins 1963).

Adams and Foulds (1962) made the point that the HOQ serves as a rating of a personality type. A quantitative scale of this sort enables one to investigate whether the degree to which a person is hysteroid or obsessoid on the scale is related to other variables.

Several researchers have demonstrated the HOQ scores of depressed patients remain stable, even after treatment, and whether or not the individual improves (Adams and Foulds 1962; Mayo 1967; Philip 1971).

Goldney and Pilowsky (1980) and Goldney (1981) examined female suicidal patients using the HOQ and LPD. They demonstrated a significant negative correlation between scores on the 2 scales, indicating that an increasing depression score significantly correlated with an increase in the obsessoid dimension of personality. However, both the HOQ and the LPD scores significantly correlated with age, and thus their association could have been an artefact. However, when a partial correlation was performed controlling for age, the strength of the association between HOQ and LPD scores, though reduced, still remained significant.

5.1.iii. The Procedure

At the initial presentation, once the patients had been selected for inclusion in the study, they were interviewed by the investigator for clinical and demographic details, and the physician rating scales were completed. Thereafter the patients filled in the self-rating questionnaires.

The scoring of all rating scales was done by the investigator. In order to assure that all calculations were correct, an experienced research assistant rechecked all scoring independently, after which any errors were corrected.

Venepunctures for assays of rbc and serum FA were performed by the investigator at the initial interview. Venepunctures in the other 2 sections of the project were also performed by the investigator when possible.

The special investigations were then conducted at times convenient to the patients, and usually took place within 6 weeks after the original presentation.

5.2. The Dexamethasone Suppression Test

5.2.i. Subjects

The first phase of the study involved 15 patients with epilepsy and a diagnosis of depression who fulfilled the criteria for the phenomenology section of the investigation. The results of this, which will be presented later, led to phase 2, which involved 14 patients with epilepsy, who were not depressed, and were being treated with various anticonvulsants which induce hepatic enzymes. These results led to the final phase which involved 10 non-depressed epileptics who were on monotherapy with VPA, which is reported not to cause hepatic enzyme induction (Oxley et al 1979; Perucca and Richens 1979).

5.2.ii. Method

One mg of dexamethasone (Oradexon; Organon Laboratories Ltd., Morden, UK) was administered orally to the subjects at 23.00 hrs. Blood samples were collected into lithium heparin tubes from the patients between 15.00 and 16.00 hrs the following day, for the estimation of cortisol. The plasma was obtained by centrifugation and stored at -20^{o}C until required for the estimation of cortisol. Cortisol was estimated using a radioimmunoassay technique (Amerlex Kit) at the MRC Neuropsychiatry Laboratory, West Park Hospital, Epsom, Surrey, which is the headquarters for a current International World Health Organisation project on the DST. Suppression, using this method, is a post DST cortisol value of 49ng/ml or less.

5.3. The Double Blind Antidepressant Trial and Pharmacokinetic Study

5.3.i. Rationale

Literature to date suggests that virtually all antidepressant drugs lower the seizure threshold and may provoke seizures clinically (Trimble 1978b; Edwards 1979). Drugs particularly implicated include amitriptyline, paradoxically one of the most widely prescribed of the antidepressants. In the study, 3 compounds were assessed, namely amitriptyline, nomifensine and placebo. A placebo was included since it is not known whether antidepressants have any clinical antidepressant action in patients with epilepsy, but in addition to assess more accurately the effect of the active compounds on the seizure threshold and to act as a control in the pharmacokinetic studies. Nomifensine was chosen to compare with amitriptyline since it has been suggested that it may not lower the seizure threshold, and may therefore prove of value in the management of depression in patients with epilepsy (Nawishy et al 1980). Moreover, as has been discussed, nomifensine is a DA agonist (Braestrup and Scheelkrüger 1976), and DA may play a role in protection against some types of reflex epilepsy (Anlezark et al 1981). Finally, nomifensine is one of the few antidepressants that has never been implicated in causing convulsions in patients (Edwards 1979).

5.3.ii. Subjects

Patients admitted to the trial had to fulfil the general epilepsy and depression criteria which qualified them for entry into the phenomenology project. However, they had to score 15 or over on the HDRS. Those with serious physical illness other than epilepsy, a progressive neurological lesion, pregnancy, those already on psychotropic medication and those for whom urgent ECT was required, were excluded from the study.

5.3.iii. Method

Patients admitted were assessed at the time of entry and prior to treatment, using the HDRS, the BDI, the STAI (State) and a side effects scale (see Appendix 11). The trial for each patient lasted 6 weeks. The mental state of the patients was assessed at every visit (at weeks 2, 4 and 6) using the same 3 rating scales; this was done at the same time in the morning at each visit, to obviate any differences caused by diurnal variation in mood. Side effects were also noted. A special clinic was set up, and patients were offered a drink of coffee and interviewed in

comfortable surroundings.

Blood was taken every 2 weeks at each visit for monitoring of both antidepressant and anticonvulsant levels, to assess their interactions. On each occasion, 2 samples were taken, 2 hours and 6 hours after the morning dose of the treatment, as the half life of nomifensine is short. Where possible, initial blood samples were taken in the mornings, otherwise at the afternoon clinic where the screening was done. In follow up, samples were taken at the same time of day, at 09.00 hrs and 13.00 hrs. On each occasion, 20ml of blood was collected by venepuncture in 2x10ml plain glass tubes, centrifuged at 3000 rpm for approximately 8 minutes. Serum was drawn off by a clean drug disposable pipette. Serum samples were deep frozen at -20°C in conventional plain glass tubes until analysis (Brunswick and Mendels 1977).

Patients were allocated in a double blind procedure, at random, to one of the 3 treatments. The hospital pharmacist kept the code and did the randomisation. The dose of the antidepressants was fixed at 25mg tid and the placebo given also on a tid basis for the 6 weeks. The capsules containing the active agents or placebo were identical in appearance. A dose of 25mg tid was chosen for nomifensine, as at the time of commencing the project it was recommended as the therapeutic dose. In addition, no trials using nomifensine in patients with epilepsy had been conducted, and no information about possible drug interactions was known. A dose of 25mg tid for amitriptyline was chosen as it was felt an initial daily dose of 150mg might result in drowsiness and consequent non-compliance and, in addition, amitriptyline might well lower seizure threshold and provoke excess abnormal EEG activity and/or a clinical attack.

Response to the 3 trial agents was ascertained, and non-response was judged clinically as failure of the HDRS to fall by 50% on the initial score. Non-responders were to have their dose doubled, and the study continued for a further 6 weeks. It was felt for ethical/clinical reasons that doubling a placebo could not be justified, and so for non-responders, the pharmacy was asked if the patient was on placebo or not. If the patient was on placebo, he or she was withdrawn from the study.

Those remaining in the next part of the study were non-responders on active agents, and their dose was doubled to 50mg tid of nomifensine or amitriptyline, double blind procedures being adhered to. The 3 rating scales, side effects scale, and twice daily blood samples were done in the same manner as during the initial trial, and were carried out for a further 6 weeks.

The serum anticonvulsant levels were measured by the department of Chemical Pathology at NHQS, who were blind to clinical details of the patients, as well as to which agent they were receiving in the double blind antidepressant trial and their dosages of anticonvulsants. The method used for the analysis of the DPH, PB, PR and CBZ concentrations was the enzyme multiplied immunoassay technique (EMIT), and the equipment was a fully automatic Gilford System 3500 with a SYVA CP 5000 microprocessor, as described by Goldberg et al (1981). Ethosuximide was measured by gas-liquid chromatography (Goldberg et al 1974) using a Perkin-Elmer F30 instrument, fitted with a flame-ionisation detector. Sodium valproate was also measured by gas-liquid chromatography, using a Perkin-Elmer F30 instrument, a method developed by Patsalos et al (1975), which is a modification of the original described by U-Schulz and Toseland (1977).

The serum antidepressant levels were measured by an independent laboratory, the staff of which were blind to clinical details of the patients and their anticonvulsant regime. The amitriptyline was determined by radioimmunoassay as described by Robinson et al (1978b), while the total nomifensine (nomifensine plus conjugates) was measured by gas chromotography (Chamberlain and Hill 1977).

The experiment was designed to answer the following questions:-

1) Are antidepressant drugs clinically effective as antidepressants in depressed patients with epilepsy?
2) Is any antidepressant effect related to serum antidepressant levels?
3) What effect does doubling the antidepressant dose have on antidepressant levels?
4) Do antidepressant drugs alter serum anticonvulsant levels?
5) Is there a relationship between serum antidepressant and anticonvulsant levels?
6) Do antidepressant drugs provoke clinical seizures in patients with epilepsy?

5.4. Statistical Analysis

The phenomenology and DST data was analysed using the Chi^2-test and Fisher's Exact Probability test for contingency tables. The Mann-Whitney U-test and Kruskal-Wallis were used for examining the relationships between discrete and continuous variables, and the Spearman correlation coefficient for pairs of continuous variables. Non-parametric tests were employed

because many of the continuous variables had non-normal distributions. In one case the Pearson partial correlation coefficient was used to investigate the relationship between 3 variables, all of which had normal distributions. The analysis of the double blind trial data also included repeated measures analysis of variance and matched paired t-tests.

The data was analysed on the CDC 6600 computer at the University of London Computer Centre. Most of the analysis was done using SPSS (Statistical Package for the Social Sciences) version 7.0. The repeated measures analysis of variance was done using BMDP (Biomedical Computer Programs P-Series, 1979 version).

Table 23 shows the symbols used in the text and tables for the various tests of significance.

TABLE 23: TESTS OF SIGNIFICANCE AND SYMBOLS USED

Test of Significance	Symbol Used
Spearman correlation coefficient	r_s
Pearson correlation coefficient	r
Pearson partial correlation coefficient	r
Kendall correlation coefficient	τ
Kruskal Wallis	KW χ^2, KWChi^2
Mann Whitney u-test	u
Chi^2	χ^2
Repeated measures analysis of variance	$F_{m,n}$
Matched pair t-test	t_n

m,n = degrees of freedom

Standard deviations will be abbreviated to SD, and degrees of freedom to df.

5.5. Ethical Considerations

The Ethical Committee of the NHQS gave permission for all sections of the investigation to be undertaken.

The aims of the studies and the procedures involved were carefully explained to all potential subjects, after which consent was obtained. No patients refused to take part in the Phenomenology Section. Two control subjects refused to participate in the DST, while 4 refused the Double Blind Antidepressant Trial.

CHAPTER 6

RESULTS

CHAPTER 6

RESULTS

6.1. The Phenomenology of Depression in Patients with Epilepsy

6.1.i. Description of the patient sample

6.1.i.a. Clinical data

Sixty-six patients fulfilled the criteria to enter the study. There were 46 females and 20 males. The age range was 18 to 67 years, with a mean of 38.1 years (SD = 12.9). Fifty-three patients were from NHQS, and 13 from the Chalfont Centre. Forty-six were out-patients, 20 in-patients.

Fifty-nine were right handed, 4 left handed and 3 ambidextrous.

The age of onset of epilepsy ranged from 1 to 57 years, with a mean of 18.88 years (SD = 11.9). Duration of epilepsy ranged from 1 to 56 years, with a mean of 19.22 years (SD = 12.6). Twenty-eight patients reported a decrease in seizure frequency prior to the onset of the depression, 28 experienced their normal frequency, while 9 had an increased frequency. Sixteen patients (24.6%) had a family history of epilepsy. Nothing was known about the family of one adopted patient.

Tables 24 and 25 show the anticonvulsants prescribed, the number of patients on the drugs, the daily dosages, the patients' serum anticonvulsant levels, and the laboratory upper limit of normal for those drugs measured. Only 3 patients were intoxicated: all 3 were receiving DPH, and their serum levels were 81, 83 and 106 μmol/litre.

Forty-three patients (65.2%) had a past history of depression. Two patients had bipolar illness. Thirteen patients were psychotic, in that they exhibited either hallucinations, delusions or both.

A positive history of psychiatric illness was found in the families of 34 (52.3%) of the patients. No details of family history were known about the one adopted patient. Table 26 shows the breakdown of family psychopathology.

TABLE 24: ANTICONVULSANTS OF PATIENTS: DAILY DOSAGES AND SERUM LEVELS

Anticonvulsant	Number of Patients On Drug	Patients Daily Doses (mg)		Serum Anticonvulsant Levels µmol/L			
				Laboratory Upper Limit of Normal	Patients Levels		
		Range	Mean		Range	Mean	SD
PB	9	60-255	123	170	28-133	83.9	32.6
PR	15	375-1000	666	60	11-49	35.3	12.4
DPH	46	100-600	298	80	13-106	48.8	24.4
CBZ	27	200-1600	800	50	8-66	30.2	13.7
VPA	7	400-2000	1000	700	130-469	326.0	153.0
Ethosuximide (ETH)	1	500	500	700	361	-	-
Sulthiame (S)	1	200	200	-	-	-	-
Clonazepam (CL)	3	1-3	1.5	-	-	-	-
Others	0	-	-	-	-	-	-

TABLE 25: BREAKDOWN OF INDIVIDUAL PATIENTS' ANTICONVULSANT MEDICATIONS

Group	Drugs	Number of Patients	
Patients on no anticonvulsants	-	1	1
Patients on monotherapy	PR	1	
	VPA	2	
	CBZ	10	27
	DPH	14	
Patients on 2 anticonvulsants	CBZ + VPA	1	
	CL + PR	1	
	PB + VPA	1	
	DPH + VPA	2	
	CBZ + PR	3	33
	DPH + PB	6	
	DPH + PR	9	
	CBZ + DPH	10	
Patients on 3 anticonvulsants	CBZ, CL, DPH	1	
	CBZ, DPH, VPA	1	4
	CL, DPH, PR	1	
	DPH, ETH, PB	1	
Patients on 4 anticonvulsants	CBZ, DPH, PB, S	1	1
TOTAL		66	

TABLE 26: PATIENTS WITH FAMILY HISTORY OF PSYCHOPATHOLOGY

Type of Psychopathology In Relatives	Number of Patients
1) Depression	8
2) Suicide	2
3) Alcoholism	3
4) Other psychiatric illness	6
5) More than one of 1-4	15

-

Type of Psychopathology	Number of Relatives
Depression	11
Alcoholism	6
Other psychiatric illness	7

The clinical seizure types of the patients are shown in Table 27.

TABLE 27: CLINICAL SEIZURE TYPES

Seizure Type	Number of Patients	Percentage of Sample	Number of Psychotics	%
Primary generalised	8	12.1	1	7.7
Secondarily generalised	9	13.6	3	23.1
Partial simple	3	4.5		
Partial complex	20	30.3	2	15.4
Partial complex, secondarily generalised	25	37.9	7	53.8
Unclassified	1	1.5		
TOTAL	66	100.0	13	100.0

6.1.i.b. Special Investigations

Psychometric assessment was completed on 57 patients. Results were as follows:-

WAIS	Range	Mean	SD
Full Scale IQ	72-118	96.87	10.82
Verbal IQ	67-119	97.41	12.58
Performance IQ	69-118	96.92	9.61

Folic acid

Fifty four patients were investigated for serum and rbc FA levels. Ten of the 12 patients who were not assessed were on FA supplement as part of their treatment regime, as they had been diagnosed previously as being FA deficient. The remainder refused venepuncture. The range of serum FA was 0.7 to 10.2ng/ml, with a mean of 2.91ng/ml (SD = 1.8). The range of rbc FA was 103 to 884ng/ml, with a mean of 322.51ng/ml (SD = 174.5).

The results of the control group showed a serum FA range from 0.4 to 25.0ng/ml, with a mean of 3.59ng/ml (SD = 2.9). The range of rbc FA was 104 to 1800ng/ml, with a mean of 551.55ng/ml (SD = 301.4).

Electroencephalographic assessment and computerised axial tomography (CAT)

The EEG assessments of patients and controls are shown in Tables 28 and 29, while the CAT scan results are shown in Table 30. Eleven patients had an intracranial lesion

TABLE 28: EEG ASSESSMENTS OF PATIENTS AND CONTROLS

EEG Category	Total Patients		Controls		Dextral Patients	
	Number	% Of Sample	Number	% Of Sample	Number	% Of Sample
Normal	6	9.1	6	9.1	6	10.2
Generalised diffuse	18	27.3	21	31.8	18	30.5
Left temporal	17	25.8	10	15.2	12	20.3
Right temporal	6	9.1	5	7.6	5	8.5
Bilateral temporal	3	4.5	1	1.5	3	5.1
Other focal	5	7.6	3	4.5	5	8.5
Non-specific abnormality	10	15.2	20	30.3	9	15.3
Unclassifiable	1	1.5	0	0	1	1.7
TOTAL	66	100.0	66	100.0	59	100.0

TABLE 29: EEG ASSESSMENTS OF PSYCHOTIC AND NON-PSYCHOTIC DEXTRAL PATIENTS

EEG Category	Psychotics	Non-Psychotics	Total
Normal	1	5	6
Generalised diffuse	2	16	18
Left temporal	2	10	12
Right temporal	1	4	5
Bilateral temporal	0	3	3
Focal other	2	3	5
Non-specific abnormality	4	5	9
Unclassifiable	0	1	1
TOTAL	12	47	59

TABLE 30: CAT SCAN DATA

Report	Number of Patients	Percentage of Sample (Adjusted Frequency)
Normal	34	58.6
Abnormal diffuse	13	22.4
Abnormal right	8	13.8
Abnormal left	2	3.4
Other	1	1.7
Missing	8	-

6.1.ii. Analysis of data

Most of the relevant results of tests of significance from the analysis of data are shown in Tables 32 to 38 which will be referred to individually when presenting results (see pages 182 to 188 at the end of this section). Important significant results not shown in these tables will also be mentioned.

The Beck Depression Inventory

The range of BDI scores was 6 to 42, with a mean of 24.85 (SD = 8.2). The significant correlations of the BDI with the other rating scales measuring affect, or aspects thereof, are shown in Table 31. (It is realised that significances given by one method would be sufficient, but the results of the 3 correlation coefficients are presented, for comparison with other published data). The highest correlations are between the BDI, the LPD depression score and A-State Anxiety, all of which are self-rating scales.

TABLE 31: CORRELATIONS OF THE BECK DEPRESSION INVENTORY WITH OTHER AFFECT RATING SCALES

Rating Scale	Spearman	Pearson	Kendall
LPD	$r_s = .57$; $p = .001$	$r = .59$; $p = .001$	$\tau = .44$; $p = .001$
HDRS (17 item)	$r_s = .38$; $p = .002$	$r = .38$; $p = .002$	$\tau = .27$; $p = .002$
HDRS (21 item)	$r_s = .39$; $p = .003$	$r = .36$; $p = .003$	$\tau = .26$; $p = .003$
STAI A-State	$r_s = .52$; $p = .001$	$r = .57$; $p = .001$	$\tau = .39$; $p = .001$
STAI A-Trait	$r_s = .29$; $p = .02$	$r = .24$; $p = .06$*	$\tau = .22$; $p = .01$
Self criticism (from HDHQ)	$r_s = .44$; $p = .008$	$r = .43$; $p = .01$	$\tau = .33$; $p = .005$
Guilt (from HDHQ)	$r_s = .41$; $p = .01$	$r = .47$; $p = .004$	$\tau = .31$; $p = .009$

* = non-significant

The BDI scores correlated significantly with the duration of epilepsy ($r_s = .31$; $p = .012$); no associations were found between BDI scores and seizure type or frequency, EEG or CAT Scan abnormality, nor the presence of an intracranial lesion (see Table 32).

Patients with a past history of depression had significantly higher BDI scores than those who were having their first depressive illness ($u = 685$; $p = .011$); patients who admitted feeling a burden to others had significantly higher BDI scores than those who did not ($u = 490$; $p = .006$); no relationships were found between BDI scores and age, sex, IQ, rbc or serum FA, handedness, family history of psychopathology, suicidal ideation or attempts, nor the presence or absence of depersonalisation, paraniod or obsessional symptoms (see Table 33).

Using the Kruskal-Wallos 1-way ANOVA, the BDI scores differed significantly according to the patients' LPD classification: those who rated as endogenously depressed had highest BDI scores, the non-endogenous depressives had intermediate scores, while those rated as not depressed had lowest scores (KW Chi^2 = 15.39; p = .0005).

On the HDHQ, those patients who rated as intropunitive had significantly higher BDI scores than the extrapunitive group (u = 133; p = .04).

LPD Depression Score (LPD-D Score)

The LPD-D scores ranged from 5 to 18 with a mean of 12.73 (SD = 3.3).

The LPD-D scores correlated significantly with the BDI (r_s = .57; p = .001), the 17 item HDRS (r_s = .38; p = .002), the 21 item HDRS (r_s = .30; p = .014) and A-State anxiety (r_s = .46; p = .001).

No relationships were found between the LPD-D score and the age of onset of epilepsy, duration of epilepsy, seizure type, nor frequency EEG or CAT Scan abnormality, nor the presence of an intracranial lesion (see Table 32).

In-patients had significantly higher LPD-D scores than did out-patients (u = 618; p = .03). Patients with a past history of depression had significantly higher LPD-D scores than those without a previous illness (u = 658; p = .03). Significantly higher LPD-D scores were found in patients with suicidal ideation and/or attempts (u = 378; p = .03) and those who reported feeling a burden to others (u = 477; p = .01). No associations were found between LPD-D scores and age, sex, IQ, serum or rbc FA, nor the presence of depersonalisation, paranoid or obsessional symptoms, nor a family history of psychopathology (see Table 33).

Hamilton Depression Rating Scale

The scores of the 17 item HDRS ranged from 12 to 30 with a mean of 19.62 (SD = 4.6), while the scores of the 21 item HDRS ranged from 13 to 33 with a mean of 21.88 (SD = 5.2). There was a significant correlation between the 17 item and 21 item HDRS scores (r_s = .94; p = .001).

No significant relationships were found between HDRS scores and age of onset of epilepsy, duration of epilepsy, seizure type nor frequency, EEG or CAT Scan abnormality, nor the presence of an intracranial lesion (see Table 32).

Patients who experienced depersonalisation, had significantly higher 17 item HDRS scores ($u = 505$; $p = .01$) and 21 item HDRS scores ($u = 563$; $p = .0004$). No significant associations between HDRS scores and age, sex, in or out-patient status, IQ, serum or rbc FA, past history of depression, family history of psychopathology, paranoid nor obsessional symptoms, nor suicidal tendencies, nor of feeling a burden to others were found (see Table 33).

The 21 item HDRS correlated significantly with the LPD-D score ($r_s = .30$; $p = .014$). Those patients who were psychotic scored significantly differently and higher than those who were not psychotic on the 17 item HDRS ($u = 471$; $p = .04$) and the 21 item HDRS ($u = 497$; $p = .01$).

The Newcastle Diagnostic Scale

The scores on this scale ranged from 1 to 10, with a mean of 4.99 (SD = 2.0), a score in the non-endogenous depression range. Twenty eight patients (42.4%) were classified as having endogenous depression, while 38 (57.6%) had non-endogenous depression.

No significant relationship was found between the Newcastle score and the LPD endo-reactive (E-R) score ($r_s = .1$; $p = .44$). There was also no significant association between the Newcastle classification and LPD classification ($Chi^2 = .56$; $p = .76$; 2 df), the number of patients in each group being presented in Table 39.

TABLE 39: CLASSIFICATION OF DEPRESSION OF PATIENTS BY THE NEWCASTLE SCALE AND LPD QUESTIONNAIRE

Newcastle Classification	LPD Classification			Total
	Endogenous Depression	Non-Endogenous Depression	Not Depressed	
Endogenous Depression	12	12	4	28
Non-Endogenous Depression	13	18	7	38
TOTAL	25	30	11	66

The Newcastle score was significantly correlated with several items of the HDHQ. The Newcastle score was significantly and positively correlated with self criticism (r_s = .44; p = .01) and direction of hostility score (r_s = .52; p = .002); that is, the higher the Newcastle score (the more endogenous), the more self criticism is reported by the patients who rate themselves as more intropunitive. The Newcastle score correlated significantly and negatively with paranoid hostility (r_s = .37; p = .03). In addition, those classified as endogenous or non-endogenous by the Newcastle scale had significantly different paranoid hostility scores: those with non-endogenous depression had higher scores (u = 90; p = .04). In addition, the Newcastle scores differed significantly between the intropunitive and extrapunitive groups on the HDHQ. The intropunitive group had higher (ie. more endogenous) scores (u = 139; p = .02).

There were significant relationships between the Newcastle classification and the presence of psychosis. Those patients who had endogenous depression were more likely to be psychotic, while those with non-endogenous depression were not psychotic (Chi^2 = 6.23; p = .01; 1 df). In addition, those who were psychotic had significantly higher (ie. more endogenous) Newcastle scores than those who were not psychotic (u = 510; p = .01).

No relationships were found between age of onset nor duration of epilepsy, seizure type nor frequency, EEG or CAT Scan abnormality, the presence of an intracranial lesion, and either the Newcastle score or classification (see Table 34).

No associations were found between the Newcastle score or classification and any of the following variables: age, sex, in or out-patient status, IQ, serum or rbc FA, handedness, personal past history of depression, family history of psychopathology, suicidal ideation, a feeling of being a burden to others, and paranoid or obsessional symptoms. Patients who had symptoms of depersonalisation had significantly higher (ie. more endogenous) scores than those who did not have depersonalisation (u = 494; p = .014) (see Table 33).

The LPD classification

The LPD score of endogenicity and non-endogenicity (LPD E-R score) ranged from -18 to +28 with a mean of +3.73 (SD = 12.6), a score in the non-endogenous range. The LPD E-R score correlated significantly and negatively with the BDI (r_s = -.26; p = .04), the LPD-D score (r_s = -.30; p = .02) and the A-State score (r_s = -.29; p = .03); ie. the more endogenous the depression, the more severe the depression and anxiety.

The LPD classifications were as shown in Table 40.

TABLE 40: THE LPD CLASSIFICATION OF THE PATIENTS' DEPRESSION

Category	Number of Patients	% Of Sample
Endogenous depression	25	37.9
Non-endogenous depression	30	45.5
Not depressed	11	16.7

The LPD classification groups were significantly related with several other mood rating scales. Using the Kruskal-Wallis 1-way ANOVA, patients with endogenous depression scored highest, those with non-endogenous depression intermediate, and those classified as not depressed scored lowest on the BDI (KW Chi^2 = 15.36; p = .001), the LPD-D score (KW Chi^2 = 17.35; p = .0002), the 17 item HDRS (KW Chi^2 = 6.44; p = .04) and A-State anxiety (KW Chi^2 = 11.81; p = .003).

There were several significant relationships between the LPD classification and the HDHQ. Non-endogenous depressives scored highest, non-depressed intermediate and endogenous depressives lowest on acting out hostility (KW Chi^2 = 7.69; p = .02). In addition there was a positive correlation between the LPD E-R score and acting out hostility (r_s = .47; p = .004). On the scores of self criticism, non-endogenous depressives scored highest, endogenous depressives intermediate and non-depressed patients lowest (KW Chi^2 = 6.02; p = .05).

There were no relationships found between the LPD E-R score and the LPD classification and age of onset of epilepsy, seizure type or frequency, EEG abnormality and presence or not of an intracranial lesion. Those patients who had abnormal CAT Scans had significantly different and lower LPD E-R scores, ie. more endogenous, ($u = 544$; $p = .03$). There was, however, a significant negative correlation between the LPD E-R score and duration of epilepsy ($r_s = -.27$; $p = .03$), that is, the longer the duration of epilepsy, the more endogenous the depression. In addition, those with endogenous depression had longer duration of epilepsy than those with non-endogenous depression ($u = 489$; $p = .05$) (see Table 34).

Significant relationships were found between the LPD E-R score, LPD classification and age, sex and in or out-patient status. There was a negative correlation between the LPD E-R score and age ($r_s = -.40$; $p = .001$); ie. the older the patient is, the more endogenous the depression. In addition, the patients who rated themselves as endogenously depressed had significantly higher ages than those who rated themselves as non-endogenously depressed ($u = 542$; $p = .005$). Moreover, using the Kruskal-Wallis 1-way ANOVA, patients who were classified as having endogenous depression had higher ages, followed by an intermediate ages of non-endogenous depression, followed by the lowest ages for non-depressives (KW $Chi^2 = 9.26$; $p = .01$). In-patients had significantly lower LPD E-R scores (more endogenous) than did out-patients ($u = 301$; $p = .03$). With regard to the LPD classification, 12 endogenously depressed patients were in-patients while 13 endogenously depressed patients were out-patients: however, significantly fewer non-endogenous depressives and non-depressed patients were in-patients ($Chi^2 = 6.74$; $p = .03$; 2 df). There were significant differences between the sexes and LPD classification: all those who scored themselves as non-depressed (11 in number) were females ($Chi^2 = 8.68$; $p = .01$; 2 df) (see Table 33). Patients who reported themselves as feeling a burden to others were significantly associated with an LPD depression classification (endogenous and non-endogenous) than non-depressed ($Chi^2 = 12.53$; $p = .002$; 2 df). In addition, all those patients except one who had suicidal ideation or attempts fell into the 2 LPD depression groups, which was significant ($Chi^2 = 10.69$; $p = .01$; 2 df) (see Table 33).

No relationships were found between LPD E-R score and classification and IQ, serum or rbc FA, handedness, personal past history of depression, family history of psychopathology nor depersonalisation, paranoid nor obsessional symptoms (see Table 33).

A significant association was found between patients who had a past history of depressive illness and complex partial seizures (Chi^2 = 5.07; p = .02; 1 df) (see Table 36).

A summary of the significant findings between mood and the epilepsy variables is presented in Table 41. The duration of epilepsy correlated significantly with the severity of depression as measured by the BDI (r_s = .31; p = .01) and significantly and negatively with the LPD E-R score (r_s = -.27; p = .03). Those with endogenous depressions on the LPD had significantly longer durations of epilepsy than those with non-endogenous depression (u = 489; p = .05). However, the LPD E-R score decreases with age, and duration of epilepsy correlated with age, so the relationship between LPD E-R score and duration of epilepsy could be because they are both related to age. To investigate this, the Pearson partial correlation coefficient between the LPD E-R score and duration of epilepsy, controlling for age, was calculated (r = -.14; p = .13): when age is taken into account the correlation between the LPD E-R score and duration is not significant. These results suggest, therefore, that the longer the duration of epilepsy, the more severe the depression, but do not support the notion that endogenicity of depression increases with duration of epilepsy. Patients with intracranial lesions had significantly higher A-State scores (u = 366; p = .05). Patients with abnormal CAT Scans had significantly different and lower LPD E-R scores, ie. more endogenous (u = 544; p = .03). No relationships were found between type and severity of depression and age of onset of epilepsy, seizure type nor frequency nor the EEG abnormality. An association was found between a past history of depression and complex partial seizures (Chi^2 = 5.07; p = .02; 1 df).

Psychosis

The presence of psychosis was found not to be related to age of onset nor duration of epilepsy, seizure type nor frequency, EEG nor CAT Scan abnormality, nor the presence or absence of an intracranial lesion (see Table 34).

No associations were found between psychosis and any of the following variables: age, sex, in or out-patient status, IQ, serum or rbc FA, handedness, personal past history of depression, family history of psychopathology, suicidal ideation or attempts, feeling a burden to others, nor symptoms of depersonalisation, obsessionalism or paranoia (see Table 33).

TABLE 41: SUMMARY OF SIGNIFICANT FINDINGS BETWEEN MOOD AND EPILEPSY VARIABLES

(Only significant results are shown)

Epilepsy Variables	Severity of Depression					Type of Depression				Past History of Depression
	BDI	LPD	17 HDRS	21 HDRS	A-State	Newcastle Score	Newcastle Classification	LPD E-R Score	LPD Classification	
Age of onset of epilepsy										
Duration of epilepsy	$r_s = .31$ $p = .01$							$r_s = -.27$ $p = .03$	$u = 489$ $p = .05$	
Seizure type										$\chi^2_1 = 5.07$ $p = .02$
EEG abnormality										
CAT Scan abnormality								$u = 544$ $p = .03$		
Seizure frequency										
Intracranial lesion					$u = 366$ $p = .05$					

State anxiety

Fifty-nine patients completed the A-State and Trait questionnaires. The scores of the A-State anxiety ranged from 30 to 78 with a mean of 58.54 (SD = 11.0).

Those patients with a past history of depression had significantly higher A-State scores than those who had no previous episodes ($u = 522$; $p = .03$). Those who felt a burden to others had significantly higher A-State scores ($u = 393$; $p = .003$). No associations were found between A-State scores and age, sex, IQ, serum or rbc FA nor patients with suicidal ideation or attempts (see Table 33).

Patients with intracranial lesions had significantly higher A-State scores ($u = 366$; $p = .05$). No relationships were found between A-State scores and age of onset or duration of epilepsy, seizure type or frequency, nor EEG or CAT Scan abnormality (see Table 32).

Trait anxiety

Scores of the A-Trait anxiety ranged from 31 to 77 with a mean of 56.19 (SD = 10.2). State and Trait anxiety scores correlated significantly ($r_s = .53$; $p = .001$). On the HDHQ, those who were intropunitive had significantly higher A-Trait scores ($u = 155$; $p = .003$).

The age of onset of epilepsy correlated significantly with Trait anxiety ($r_s = .31$; $p = .01$). No associations between Trait anxiety and duration of epilepsy, seizure type or frequency, EEG or CAT Scan abnormality were found (see Table 35).

Neuroticism

Sixty-six patients filled in the EPI; there were 2 spoiled questionnaires. The N scores on the EPI ranged from 5 to 23 with a mean of 15.70 (SD = 4.3). Table 42 shows the correlations between N scores and various affect variables.

TABLE 42: NEUROTICISM SCORES CORRELATING WITH ASPECTS OF AFFECT

Aspect of Affect	Rating Scale	Spearman Correlation Coeffieient
Severity of depression	17 item HDRS	$r_s = .37$; $p = .003$
	21 item HDRS	$r_s = .44$; $p = .001$
Anxiety	STAI State	$r_s = .28$; $p = .03$
	STAI Trait	$r_s = .45$; $p = .001$
Hostility	HDHQ - hostility sum	$r_s = .43$; $p = .01$
	- paranoid hostility	$r_s = .52$; $p = .002$
	- acting out hostility	$r_s = .43$; $p = .01$

No significant relationships were found between N scores and age of onset or duration of epilepsy, seizure type nor frequency, EEG or CAT Scan abnormality, nor the presence of an intracranial lesion (see Table 35).

Out-patients had significantly higher N scores on the EPI than did in-patients ($u = 270$; $p = .02$). Patients who had symptoms of depersonalisation had significantly higher N scores ($u = 485$; $p = .003$). No associations were found between N scores and age, sex, IQ, serum or rbc FA, handedness, a past history of depression, family psychopathology, paranoid or obsessional symptoms, suicidal ideation or attempts nor a feeling of being a burden to others (see Table 33).

Extraversion

The E scores ranged from 3 to 21 with a mean of 9.88 (SD = 3.8).

Extraversion scores were significantly and negatively correlated with STAI Trait anxiety ($r_s = -.50$; $p = .001$) and the direction of hostility on the HDHQ ($r_s = .45$; $p = .01$); that is, the more extravert, the less trait anxiety and the more extrapunitive. The E score was significantly and positively correlated with the HOQ score ($r_s = .53$; $p = .001$); that is, the more extravert, the more hysteroid the individual.

Extraversion scores did not correlate with age of onset nor duration of epilepsy, seizure type nor frequency, EEG or CAT Scan abnormality nor the presence of an intracranial lesion (see Table 35).

The Lie scores of the EPI ranged from 0 to 7 with a mean of 3.17 (SD = 1.7).

The Hysteroid/Obsessoid Questionnaire

The scores on the HOQ ranged from 8 to 36, with a mean of 19.58 (SD = 5.4), which falls into the obsessoid range. Fifty three patients were classified as obsessoid, while 13 were hysteroid.

Patients who had suicidal ideation or attempts had significantly lower, ie. more obsessoid scores ($u = 701$; $p = .04$).

There was no relationship found between the HOQ score and obsessional traits (from the HDRS), ($u = 390$; $p = .7$).

There were several significant associations between the HOQ scores and aspects of the HDHQ. Scores of the HOQ correlated significantly and positively with criticism of others ($r_s = .38$; $p = .02$), sum of hostility ($r_s = .35$; $p = .04$). and negatively with the direction of hostility ($r_s = -.40$; $p = .02$). Obsessoid patients had significantly lower sum of hostility scores ($u = 56$; $p = .02$) and significantly lower acting out of hostility scores ($u = 44$; $p = .004$).

Obsessoids had significantly lower extraversion scores on the EPI than did hysteroid patients ($u = 154$; $p = .003$).

No relationships were found between HOQ score or classification and age of onset or duration of epilepsy, seizure type or frequency, EEG or CAT Scan abnormality or the presence of an intracranial lesion (see Table 35).

Hostility and Direction of Hostility Questionnaire

This questionnaire was completed by 36 patients and the range of scores, means and standard deviations are presented in Table 43.

TABLE 43: RESULTS OF THE HDHQ

Item	Range	Mean	Standard Deviation
Acting out hostility	1 to 12	5.53	2.7
Criticism of others	1 to 10	5.69	2.4
Projected hostility	0 to 6	1.67	1.4
Self criticism	3 to 11	7.67	2.7
Guilt	0 to 7	3.42	2.0
Sum of hostility	11 to 36	23.97	7.0
Direction of hostility score	-12 to +24	+5.86	7.2

Twenty-nine (82.9%) of patients were intropunitive, while 6 (17.1%) were extrapunitive.

Significant correlations between subscales of the HDHQ and ratings of severity of depression and anxiety are presented in Table 44.

TABLE 44: SIGNIFICANT RELATIONSHIPS BETWEEN HDHQ, SEVERITY OF DEPRESSION AND ANXIETY SCORES

HDHQ Subscale	BDI	17-HDRS	A-State	A-Trait
Self criticism	$r_s = .44^{**}$	NS	$r_s = .43^{**}$	$r_s = .52^{**}$
Guilt	$r_s = .41^{**}$	NS	$r_s = .48^{**}$	$r_s = .47^{**}$
Paranoid hostility	NS	$r_s = .34^{*}$	NS	NS
Criticism of others	NS	NS	NS	NS
Sum of hostility score	NS	NS	$r_s = .48^{**}$	$r_s = .35^{*}$
Direction of hostility score	NS	NS	NS	$r_s = .43^{**}$

NS : non-significant

* : $p < .05$

** : $p < .01$

TABLE 45: INTERCORRELATIONS OF THE SUBSCALES OF THE HDHQ

HDHQ Subscales	SC	G	AH	PH	CO	H-Sum
Self criticism (SC)	-					
Guilt (G)	$r_s = .71^{***}$	-				
Acting out of hostility (AH)	NS	NS	-			
Projected hostility (PH)	NS	NS	$r_s = .39^{*}$	-		
Criticism of others (CO)	NS	NS	$r_s = .56^{***}$	$r_s = .34^{*}$	-	
Hostility sum (H-Sum)	$r_s = .70^{***}$	$r_s = .59^{***}$	$r_s = .69^{***}$	$r_s = .49^{**}$	$r_s = .76^{***}$	-
Hostility direction	$r_s = .62^{***}$	$r_s = .65^{***}$	$r_s = -.46^{**}$	$r_s = -.33^{*}$	NS	NS

NS : non-significant
* : $p < .05$
** : $p < .01$
*** : $p < .001$

Depression scores were correlated significantly with guilt, self criticism and paranoid hostility; anxiety scores were correlated with guilt, self criticism, criticism of others, sum of hostility and direction of hostility scores.

Using the Mann-Whitney U-test, those patients who reported themselves as feeling a burden to others on the LPD had significantly different and higher self criticism ($u = 134$; $p = .01$), guilt ($u = 138$; $p = .01$) and direction of hostility, ie. more intropunitive, ($u = 138$; $p = .01$) scores.

The internal consistency of the HDHQ is shown by the significant correlations presented in Table 45.

In addition, using the Mann-Whitney U-test, patients who were intropunitive had higher guilt scores ($u = 157$; $p = .002$).

Several relationships were found between HDHQ scores and epilepsy variables. Those patients who reported an increased seizure frequency had higher self criticism scores than those who reported a decreased seizure frequency, who, in turn, had higher scores than those with a normal frequency (KW $Chi^2 = 7.02$; $p = .03$); the same pattern was found between seizure frequency and guilt (KW $Chi^2 = 6.75$; $p = .03$) and direction of hostility (KW $Chi^2 = 6.5$; $p = .04$) scores. Patients with abnormal scans had higher paranoid hostility scores ($u = 56$; $p = .01$). Those with intracranial lesions had significantly higher criticism of others ($u = 163$; $p = .01$) and sum of hostility ($u = 165$; $p = .01$) scores. No associations were found between HDHQ scores and age of onset or duration of epilepsy, seizure type nor EEG abnormality (see Table 35).

Depersonalisation

On the 21 item HDRS, 13 patients had the symptom of depersonalisation, while 53 did not.

Patients reporting depersonalisation were judged as significantly more depressed on both the 17 item HDRS ($u = 505$; $p = .01$) and the 21 item HDRS ($u = 563$; $p = .0004$). Patients with depersonalisation had more endogenous scores on the Newcastle scale ($u = 494$; $p = .01$) and higher neuroticism scores on the EPI ($u = 485$; $p = .003$) (see Table 33).

Patients with depersonalisation scored significantly lower on criticism of others ($u = 9.0$; $p = .002$), significantly higher on self criticism ($u = 125$; $p = .03$) and significantly higher on direction of hostility, ie. were more intropunitive ($u = 155$; $p = .0004$), on the HDHQ.

Significantly more patients with depersonalisation had normal CAT Scans ($Chi^2 = 5.20$; $p = .02$; 1 df). No associations were found between depersonalisation and age of onset or duration of epilepsy, seizure type nor frequency, nor EEG abnormality (see Table 36).

Paranoid Symptoms

On the 21 item HDRS, 22 patients had paranoid symptoms, while 44 did not.

Paranoid symptoms were found not to be associated with either type or severity of depression (see Table 33).

Those who were paranoid had significantly earlier ages of onset of epilepsy ($u = 297$; $p = .01$), but no associations were found between seizure type nor frequency, EEG nor CAT Scan abnormality (see Table 36).

Obsessionality

On the 21 item HDRS, 17 patients were rated as having obsessional symptoms, while 49 were not.

No associations were found between obsessional symptomatology and severity or type of depression (see Table 33) nor the age of onset or duration of epilepsy, seizure type nor frequency nor EEG abnormality (see Table 36).

Suicidal behaviour

The presence of this was derived from the HDRS and BDI. Table 46 shows the breakdown of findings.

TABLE 46: SUICIDAL IDEATION AND ATTEMPTS (SUICIDAL BEHAVIOUR)

Category	Number of Patients	% of Sample
Suicidal attempts	7	10.6
Suicidal ideation	27	40.9
Neither	32	48.5

Those with suicidal behaviour had significantly higher depression scores on the LPD ($u = 378$; $p = .03$) and were over-represented in the depressive groups of the LPD ($Chi^2 = 10.69$; $p = .005$; 2 df); no associations were found between suicidal behaviour and type of depression nor presence of psychosis (see Table 33).

No relationships between suicidal behaviour and age of onset or duration of epilepsy, seizure type nor frequency nor EEG abnormality were found (see Table 36).

Those who had suicidal behaviour had significantly different and lower scores on the HOQ ($u = 702$; $p = .05$) than patients without ie. suicidal behaviour was associated with increasing obsessionality.

The feeling of being a "burden to others"

This item from the LPD questionnaire was analysed separately as it was felt that it may be attributed to depression or a chronic illness such as epilepsy. Fifty-four patients (81.8%) felt a burden to others, while 12 patients (18.2%) did not.

Patients who felt "a burden to others" had significantly higher BDI scores ($u = 490$; $p = .01$), LPD-D scores ($u = 477$; $p = .01$) and A-State scores ($u = 393$; $p = .003$). In addition, those who felt "a burden to others" were significantly overrepressed in the 2 types of LPD depression categories, as compared with the non-depressed group ($Chi^2 = 12.53$; $p = .002$; 2 df) (see Table 33).

Those who felt "a burden to others", had, on the HDHQ, significantly higher self criticism ($u = 134$; $p = .01$) and guilt ($u = 138$; $p = .01$) scores, and were significantly more intropunitive ($u = 138$; $p = .01$). The STAI-Trait scores of the patients were also significantly higher ($u = 369$; $p = .01$).

No relationship was found between feeling "a burden to others" and either a previous depressive illness ($Chi^2 = .78$; 1 df) or suicidal ideation or behaviour ($Chi^2 = .19$; 1 df). No association was found between age and the feeling of "a burden to others" ($u = 362$; $p = .53$).

Feeling "a burden to others" was found to have no relationship with age of onset or duration of epilepsy, seizure type or frequency, EEG or CAT Scan abnormality (see Table 36).

Age

The age of patients correlated with the age of onset of epilepsy ($r_s = .45$; $p = .001$) and the duration of epilepsy ($r_s = .52$; $p = .001$). No associations were found between age and severity of depression nor anxiety, nor with any personality ratings. On the HDHQ, the intropunitive group of patients were significantly older ($u = 134$; $p = .04$).

Family history of psychiatric illness

Patients with a family history of psychopathology differed in their HOQ classification: the hysteroid group was significantly associated with a family history of psychopathology ($Chi^2 = 5.28$; $p = .02$; 1 df). In addition, on the HDHQ, those patients with a family history of psychopathology had significantly higher acting out hostility scores ($u = 224$; $p = .05$). No relationships were found between having a family history of psychopathology and type or severity of depression, presence or absence of psychosis, nor any aspect of epilepsy.

Age of onset of epilepsy

There was a significant negative correlation between age of onset of epilepsy and duration of epilepsy (r_s = -.37; p = .003), (see Table 38). Males had a significantly higher mean age of onset than females (u = 619; p = .026; 2 df), (see Table 36). Patients who had higher mean age of onset of epilepsy had abnormal CAT Scans (u = 276; p = .036; 2 df), (see Table 38).

The age of onset of epilepsy was significantly correlated with trait anxiety (r_s = .31; p = .017), (see Table 35). Patients with a higher age of onset of epilepsy were significantly more paranoid as judged by the HDRS (u = 297; p = .01; 2 df), (see Table 36).

The age of onset of epilepsy was not significantly associated with type nor severity of depression (see Tables 32 and 34).

EEG analysis

Table 28 shows the EEG assessments of the 66 patients, and the 66 age and sex matched control epileptic patients with no psychiatric impairment.

There were no significant differences between the 2 groups (Chi^2 = 8; p = .33; 7 df). It can be seen, however, that there is a bias towards left temporal abnormalities in both groups, though more marked in the patient group. In addition, in the control group there were double the number of subjects with non-specific EEG abnormalities (20 in the control group, 10 in the patient group).

It can be seen from Table 29 that of all dextral patients who had spike and wave abnormalities on their EEGs, fewer than half had temporal lobe lesions. Of the 12 psychotic dextral patients, 3 had temporal lobe lesions, of which one was right sided.

Folic acid

Using the Mann-Whitney U-test, there were significant differences between the patient and control groups for both serum FA (u = 5751; p = .04) and rbc FA (u = 7317; p = .0001). The patients had significantly lower levels in both instances.

Using the Mann-Whitney U-test, patients with complex partial seizures had significantly lower serum FA than did those patients with generalised epilepsy ($u = 402$; $p = .012$). However, no significant relationships between either serum or rbc FA and age of onset of epilepsy, duration of epilepsy, EEG abnormality, CAT Scan abnormality nor seizure frequency were found (see Table 36).

No associations were found between serum or rbc FA and severity nor type of depression, nor the presence or absence of psychosis (see Table 33).

Anticonvulsant drugs and mood

Table 37 shows the main relationships between anticonvulsant drugs and mood.

Phenobarbitone

Nine patients were being treated with PB: none were on monotherapy. Patients taking PB reported themselves as being significantly more depressed on the BDI than those not taking the drug ($u = 373$; $p = .03$). Patients receiving PB were judged as being significantly more depressed using the 17 item HDRS ($u = 363$; $p = .05$). There was a significant negative correlation between PB dose and BDI score ($r_s = -.67$; $p = .05$). Patients who were paranoid had significantly higher PB levels than those who were not paranoid ($u = 30$; $p = .035$). There were no relationships between PB dose, level or having the drug and type of depression, state or trait anxiety, presence of psychosis, extraversion, neuroticism nor hostility variables. There was no significant relationship between PB dose and PB level ($r_s = .32$; $p = .68$).

Primidone

Fourteen patients were treated with PR: one was on monotherapy. Patients receiving PR had significantly lower scores on the 21 item HDRS ($u = 242$; $p = .031$) than those who were not treated with the drug. Those patients treated with PR were less intropunitive on the HDHQ ($u = 104$; $p = .041$). The PR doses correlated significantly with PR levels ($r_s = .65$; $p = .04$).

Carbamazepine

Twenty-seven patients were treated with CBZ: ten were on monotherapy. Patients receiving CBZ rated themselves as significantly less depressed on the LPD ($u = 361$; $p = .03$). With regard to type of depression, significantly less patients on CBZ reported themselves as depressed on the LPD (including both endogenous and non-endogenous depressions), while significantly more rated themselves as non-depressed ($Chi^2 = 9.34$; $p = .01$; 2 df). Patients receiving CBZ reported significantly lower A-Trait anxiety scores than those not receiving the drug ($u = 272$; $p = .02$). Moreover, there were statistcially significant negative correlations between trait anxiety scores and both CBZ dose ($r_s = -.48$; $p = .02$) and CBZ level ($r_s = -.52$; $p = .04$). There was a significant positive correlation between CBZ dosages and levels ($r_s = .67$; $p = .002$).

On the HDHQ, patients on CBZ had lower direction of hostility scores ie. they were more extrapunitive and less intropunitive ($u = 193$; $p = .02$). Significantly less patients on CBZ rated themselves as intropunitive, while significantly more patients on CBZ rated themselves as extrapunitive ($Chi^2 = 3.7$; $p = .05$; 1 df). Patients receiving CBZ reported themselves as less guilty ($u = 95$; $p = .04$).

Phenytoin

Forty-six patients were being treated with DPH: fourteen were on monotherapy. Patients receiving DPH reported higher self criticism on the HDHQ than those not on DPH ($u = 211$; $p = .04$).

Valproic acid

Seven patients were receiving VPA: two were on monotherapy. No relationships were found between any aspect of mood and VPA.

No associations were found between anticonvulsants and type of depression as rated by either the Newcastle scale or LPD, the presence of psychosis, nor the degree of extraversion or neuroticism.

So few patients received ethosuximide, sulthiame and clonazepam, that it was felt inappropriate to perform tests of significance as regards mood and the taking of the drugs.

Intercorrelations between epilepsy variables

The age of onset of epilepsy correlated negatively and significantly with the duration of epilepsy (r_s = -.37; p = .003). Those patients with abnormal CAT Scans had significantly higher ages of onset of epilepsy than those with normal scans (u = 276; p = .04). All 11 patients with an intracranial lesion had abnormal scans, which is highly significant (Chi^2 = 16.36; p = .0001; 1 df), (see Table 38).

The age of onset of epilepsy was not found to be associated with seizure type nor frequency, EEG abnormality nor presence of an intracranial lesion. Duration of epilepsy was found to have no relationship with seizure type nor frequency, EEG or CAT Scan abnormality nor the presence of an intracranial lesion. There were no associations found between the seizure type and seizure frequency, EEG or CAT Scan abnormality nor presence of an intracranial lesion. EEG abnormality was not found to be related to seizure frequency, CAT Scan abnormality nor presence of an intracranial lesion. No relationship was found between CAT Scan abnormality and seizure frequency (see Table 38).

Table 32 RELATIONSHIPS BETWEEN SEVERITY OF DEPRESSION & EPILEPSY

Epilepsy Variables	RATING SCALES				
	BDI	LPD-D Score	HDRS (17 item)	HDRS (21 item)	STAI State
Age of onset of Epilepsy	r_s=−.11	r_s=−.05	r_s=−.12	r_s=−.13	r_s=−.07
Duration of Epilepsy	r_s=.31*	r_s=.13	r_s=.06	r_s=.02	r_s=.18
Clinical type of Seizure	u=412	u=466	u=438	u=440	u=330
EEG Abnormality	u=442	u=317	u=353	u=382	u=282
CAT Scan Abnormality	u=370	u=356	u=406	u=440	u=301
Seizure frequency	K-W χ^2=1.39	K-W χ^2=2.21	K-W χ^2=.31	K-W χ^2=.74	K-W χ^2=.89
Intracranial lesion	u=387	u=392	u=300	u=288	u=366*

* $p < .05$

** $p < .01$

Table 33 RELATIONSHIPS BETWEEN TYPE & SEVERITY OF DEPRESSION & MISCELLANEOUS VARIABLES

Miscellaneous Variables	DEPRESSION SEVERITY RATING SCALES					TYPE OF DEPRESSION RATING SCALES				Presence of Psychosis	Neuroticism Score
	BDI	LPD-D Score	HDRS (17 item)	HDRS (21 item)	STAI State	Newcastle Class.	Newcastle Score	LPD E-R Score	LPD Class.		
Age	r_s=.17	r_s=.13	r_s=.03	r_s=−.01	r_s=.10	u=459	r_s=−.04	r_s=−.40**	u=542**	u=336	r_s=−.16
Sex	u=394	u=456	u=506	u=490	u=354	χ^2_1=.30	u=533	u=363	χ^2_2=8.68**	χ^2_1=.14	u=412
Inpatient/ Outpatient	u=548	u=618*	u=421	u=390	u=357	χ^2_1=2.67	u=583	u=301*	χ^2_2=6.74*	χ^2_1=1.1	u=270*
Full scale IQ	r_s=.01	r_s=−.02	r_s=−.003	r_s=.09	r_s=.05	u=384	r_s=−.13	r_s=−.04	u=293	u=273	r_s=−.11
Verbal IQ	r_s=.08	r_s=−.01	r_s=−.003	r_s=.09	r_s=.16	u=374	r_s=−.13	r_s=−.08	u=297	u=269	r_s=−.12
Performance IQ	r_s=−.15	r_s=−.15	r_s=.005	r_s=.11	r_s=−.13	u=385	r_s=−.07	r_s=−.04	u=267	u=258	r_s=−.1
rbc folate	r_s=−.14	r_s=−.07	r_s=−.11	r_s=−.04	r_s=−.14	u=330	r_s=−.12	r_s=.19	u=214	u=192	r_s=.02
Serum folate	r_s=−.09	r_s=−.23	r_s=−.16	r_s=−.14	r_s=−.06	u=326	r_s=−.05	r_s=.12	u=231	u=230	r_s=−.12
Handedness	u=144	u=159	u=150	u=179	u=137	χ^2_1=.18	u=195	u=249	χ^2_1=.04	χ^2_1=.01	u=194
Personal past History of Depression	u=685**	u=658*	u=584	u=563	u=522*	χ^2_1=1.39	u=588	u=354	χ^2_2=4.66	χ^2_1=.45	u=456
Family History of Psychopathology	u=556	u=533	u=558	u=569	u=479	χ^2_5=7.3	u=406	u=577	χ^2_{10}=13.28	χ^2_1=.03	u=563
Depersonalisation symptoms	u=357	u=308	u=505**	u=563***	u=211	χ^2_1=1.54	u=494**	u=366	χ^2_2=.02	χ^2_1=2.28	u=485
Paranoid symptoms	u=532	u=424	u=459	u=576	u=345	χ^2_1=.008	u=508	u=474	χ^2_2=.89	χ^2_1=2.02	u=487
Obsessional symptoms	u=405	u=446	u=450	u=519	u=314	χ^2_1=.16	u=363	u=474	χ^2_2=1.66	χ^2_1=1.71	u=489
Suicidal behaviour	u=427	u=378*	u=439	u=470	u=369	χ^2_1=.001	u=478	u=498	χ^2_2=10.69**	χ^2_1=.01	u=545
Burden to others	u=490**	u=477**	u=373	u=378	u=393**	χ^2_1=2.8	u=432	u=373	χ^2_2=12.53**	χ^2_1=.48	u=363

* $p < .05$

** $p < .01$

*** $p < .001$

Table 34 RELATIONSHIPS BETWEEN TYPE OF DEPRESSION & EPILEPSY

Epilepsy Variables	RATING SCALES				Presence of Psychosis
	Newcastle Score	Newcastle Classification	LPD E-R Score	LPD Classification	
Age of onset of Epilepsy	r_s=–.10	u=435	r_s=–.11	u=411	u=286
Duration of Epilepsy	r_s=.07	u=536	r_s=–.27*	u=489*	u=352
Clinical type of Seizure	u=303	χ^2_1=1.19	u=426	χ^2_2=2.27	χ^2_1=.002
EEG Abnormality	u=433	χ^2_1=.07	u=362	χ^2_2=4.6	χ^2_1=.26
CAT Scan Abnormality	u=450	χ^2_1=.05	u=544*	χ^2_2=4.51	χ^2_1=.09
Seizure frequency	K-W χ^2=2.28	χ^2_2=2.02	K-W χ^2=3.93	χ^2_4=3.92	χ^2_2=.49
Intracranial lesion	u=371	χ^2_1=1.5	u=275	χ^2_2=.7	χ^2_1=.08

* $p < .05$

Table 35 RELATIONSHIPS BETWEEN PERSONALITY & EPILEPSY

Epilepsy Variables	RATING SCALES												
	STAI State	HOQ		HDHQ								EPI	
		Score	Classification	AH	CO	PH	SC	G	Hostility Sum	Direction of Hostility Score	Direction of Hostility Classification	Extraversion	Neuroticism
Age of onset of Epilepsy	r_s=.31*	r_s=-.02	u=361	r_s=-.05	r_s=-.15	r_s=-.11	r_s=.21	r_s=.12	r_s=.04	r_s=.30	u=116	r_s=-.16	r_s=-.02
Duration of Epilepsy	r_s= .12	r_s=-.01	u=394	r_s=-.27	r_s=.06	r_s=-.23	r_s=-.14	r_s=.008	r_s=-.14	r_s=.05	u=106	r_s=.11	r_s=-.13
Clinical type of Seizure	u=400	u=265	χ^2_1=.32	u=107	u=102	u=99	u=79	u=91	u=92	u=66	χ^2_1=.23	u=288	u=475
EEG Abnormality	u=342	u=448	χ^2_1=.05	u=111	u=90	u=124	u=85	u=111	u=96	u=99	χ^2_1=.11	u=314	u=467
CAT Scan Abnormality	u=361	u=322	χ^2_1=.12	u=121	u=86	u=56**	u=109	u=115	u=84	u=143	χ^2_1=.07	u=275	u=442
Seizure frequency	K-W χ^2=.22	K-W χ^2=.53	χ^2_2=1.04	K-W χ^2=4.35	K-W χ^2=.001	K-W χ^2=2.37	K-W χ^2=7.02*	K-W χ^2=6.75*	K-W χ^2=1.67	K-W χ^2=6.5*	χ^2_2=2.04	K-W χ^2=2.88	K-W χ^2=.38
Intracranial lesion	u=308	u=359	χ^2_1=.08	u=129	u=163**	u=142	u=144	u=132	u=165**	u=101	χ^2_1=.11	u=273	u=258

* $p < .05$

** $p < .01$

Table 36 RELATIONSHIPS BETWEEN EPILEPSY & MISCELLANEOUS VARIABLES

Miscellaneous Variables	Age of Onset of Epilepsy	Duration of Epilepsy	Clinical Seizure Type	EEG Abnormality	Seizure Frequency	CAT Scan Abnormality	Intracranial Lesion
Age	r_S=.45***	r_S=.52***	u=331	u=475	K-W χ^2=.78	u=287	u=292
Sex	u=619*	u=407	χ^2_1=4.13*	χ^2_1=.84	χ^2_2=.79	χ^2_1=3.09	χ^2_1=.70
Inpatient/ Outpatient	u=454	u=666**	χ^2_1=5.25*	χ^2_1=.24	χ^2_2=1.47	χ^2_1=2.09	χ^2_1=.70
Full scale IQ	r_S=.02	r_S=−.14	u=277	u=419*	K-W χ^2=.02	u=349	u=219
Verbal IQ	r_S=−.01	r_S=−.11	u=286	u=408*	K-W χ^2=.01	u=351	u=207
Performance IQ	r_S=−.0005	r_S=−.12	u=229	u=349	K-W χ^2=1.13	u=324	u=197
rbc folate	r_S=.25	r_S=−.24	u=255	u=332	K-W χ^2=1.97	u=362	u=181
Serum folate	r_S=.06	r_S=−.16	u=402**	u=361	K-W χ^2=1.26	u=361	u=193
Handedness	u=197	u=185	χ^2_1=.02	χ^2_1=3.84*	χ^2_2=.001	χ^2_1=.17	χ^2_1=.13
Personal past History of Depression	u=440	u=711**	χ^2_1=5.07*	χ^2_1=.02	χ^2_2=2.7	χ^2_1=.05	χ^2_1=.21
Family History of Psychopathology	u=490	u=443	χ^2_1=1.13	χ^2_1=.09	χ^2_2=.47	χ^2_1=.06	χ^2_1=.24
Depersonalisation	u=382	u=259	χ^2_1=1.83	χ^2_1=.05	χ^2_2=2.95	χ^2_1=5.20*	χ^2_1=1.91
Paranoid symptoms	u=297**	u=560	χ^2_1=.0001	χ^2_1=.02	χ^2_2=2.94	χ^2_1=1.48	χ^2_1=.01
Obsessional symptoms	u=469	u=418	χ^2_1=.33	χ^2_1=3.07	χ^2_2=1.9	χ^2_1=.28	χ^2_1=.06
Suicidal behaviour	u=604	u=584	χ^2_1=.32	χ^2_1=.02	χ^2_2=1.13	χ^2_1=2.04	χ^2_1=1.47
Burden to others	u=298	u=399	χ^2_1=.02	χ^2_1=.05	χ^2_2=3.34	χ^2_1=1.76	χ^2_1=.18

* $p < .05$

** $p < .01$

*** $p < .001$

Table 37 RELATIONSHIPS BETWEEN ANTICONVULSANTS AND MOOD

Anticonvulsant Variables		DEPRESSION SEVERITY RATING SCALES					TYPE OF DEPRESSION RATING SCALES				Presence of Psychosis	STAI TRAIT	HDHQ			EPI	
		BDI	LPD-D Score	HDRS (17 item)	HDRS (21 item)	STAI STATE	Newcastle Class.	Newcastle Score	LPD Class.	LPD E-R Score			Direction Score	Guilt	Self Criticism	E	N
PB	Dose	r_s=−.67*	r_s=.13	r_s=−.41	r_s=−.29	r_s=−.31	u=13	r_s=.09	u=4	r_s=.44	u=3	r_s=−.31	r_s=−.06	r_s=−.11	r_s=−.63	r_s=.29	r_s=−.04
	Level	r_s=−.12	r_s=−.02	r_s=−.01	r_s=.02	r_s=−.31	u=10	r_s=.08	u=7	r_s=.22	N/A	r_s=−.18	r_s=.05	r_s=.01	r_s=−.15	r_s=.24	r_s=−.12
	Yes/No	u=373*	u=262	u=363*	u=354	u=247	χ^2_1=.05	u=301	χ^2_1=.01	u=325	χ^2_1=.06	u=205	u=83	u=84	u=87	u=233	u=264
DPH	Dose	r_s=−.16	r_s=−.13	r_s=−.04	r_s=−.08	r_s=.04	u=310	r_s=.07	u=197	r_s=−.02	u=117	r_s=−.1	r_s=−.16	r_s=−.08	r_s=−.28	r_s=.14	r_s=−.12
	Level	r_s=.03	r_s=−.26	r_s=.06	r_s=.13	r_s=−.17	u=91	r_s=−.11	u=47	r_s=.08	u=42	r_s=−.29	r_s=−.15	r_s=−.1	r_s=.12	r_s=−.37	r_s=.01
	Yes/No	u=500	u=448	u=500	u=534	u=363	χ^2_1=.3	u=493	χ^2_1=.02	u=523	χ^2_2=2.97	u=426	u=188	u=203	u=211*	u=510	u=466
PR	Dose	r_s=−.25	r_s=−.26	r_s=−.16	r_s=−.20	r_s=.14	u=14	r_s=.13	u=29	r_s=−.24	u=4	r_s=−.18	N/A	r_s=.06	r_s=.28	r_s=.34	r_s=.08
	Level	r_s=.25	r_s=−.23	r_s=−.58	r_s=−.46	r_s=.07	u=9	r_s=.35	u=6	r_s=−.55	N/A	r_s=−.41	r_s=.83**	r_s=.25	r_s=.64	r_s=−.17	r_s=−.45
	Yes/No	u=405	u=458	u=283	u=242*	u=357	χ^2_1=2.90	n=276	χ^2_1=1.34	u=441	χ^2_1=1.15	u=375	u=175	u=192	u=185	u=333	u=310
CBZ	Dose	r_s=−.32	r_s=−.1	r_s=.13	r_s=.08	r_s=−.11	u=93	r_s=.05	u=33	r_s=.15	u=53	r_s=−.48*	r_s=−.24	r_s=.06	r_s=−.27	r_s=.18	r_s=−.09
	Level	r_s=−.31	r_s=.17	r_s=.21	r_s=.12	r_s=.14	u=59	r_s=.2	u=22	r_s=−.36	u=35	r_s=−.52*	r_s=.09	r_s=.10	r_s=.01	r_s=.20	r_s=−.30
	Yes/No	u=394	u=361*	u=391	u=425	u=340	χ^2_1=1.1	u=589	χ^2_2=9.34**	u=493	χ^2_1=.55	u=272*	u=113	u=95*	u=107	u=542	u=533
VPA	Dose	r_s=−.58	r_s=−.67	r_s=−.16	r_s=−.15	r_s=−.52	u=3	r_s=−.34	u=2	r_s=.13	u=2	r_s=−.55	N/A	N/A	N/A	r_s=.55	r_s=−.13
	Level	r_s=−.29	r_s=−.37	r_s=.14	r_s=.09	r_s=−.70	u=4	r_s=.14	u=1	r_s=−.14	N/A	r_s=−.6	N/A	N/A	N/A	r_s=.15	r_s=.14
	Yes/No	u=174	u=196	u=213	u=246	u=184	χ^2_1=.18	u=240	χ^2_1=.04	u=238	χ^2_1=.01	u=202	u=13	u=27	u=30	u=148	u=242

* $p < .05$

** $p < .01$

N/A = not applicable : too few cases

Table 38 EPILEPSY INTERRELATIONSHIPS

Epilepsy Variables	Age of Onset of Epilepsy	Duration of Epilepsy	Seizure type	EEG Abnormality	Seizure Frequency	CAT Scan Abnormality	Intracranial Lesion
Age onset of Epilepsy	—						
Duration of Epilepsy	r_s=–.37**	—					
Seizure Type	u=409	u=311	—				
EEG Abnormality	u=485	u=427	χ^2_1=1.18	—			
Seizure frequency	K-W χ^2=.33	K-W χ^2=.93	χ^2_2=4.52	χ^2_2=2.06	—		
CAT Scan Abnormality	u=276*	u=431	χ^2_1=1.03	χ^2_1=.04	χ^2_2=2	—	
Intracranial lesion	u=406	u=210	χ^2_1=.35	χ^2_1=.05	Fishers exact probability p >.05	χ^2_1=16.36****	—

* p <.05

** p <.01

**** p <.0001

6.2. The Dexamethasone Suppression Test (DST)

6.2.i. Description of the sample

6.2.i.a. Clinical data

Patients

Fifteen depressed epileptics fulfilling the same criteria as for the "phenomenology" study formed the experimental group. On the Newcastle diagnostic scale, 7 were classified as endogenously depressed and 8 were rated as having non-endogenous depression. Using the LPD, 8 were classified as endogenously depressed, 4 as non-endogenously depressed, and 3 as not depressed. The number of patients on one or more of the following anticonvulsants are indicated in brackets: PB (1); DPH (9); PR (3); CBZ (8); Clonazepam (1); VPA (2). No person was on VPA monotherapy. The rest of the clinical details are presented in Table 47.

Controls

There were 2 control groups.

The first consisted of 14 non-depressed epileptics (Group A) who were being treated with one or more anticonvulsant agents which are known to induce hepatic enzymes. The following anticonvulsants were used, the number of control subjects on the drug being shown in brackets: PB (3); DPH (7); PR (5); CBZ (8); VPA (4). No person was on VPA monotherapy. Clinical details of the subjects are shown in Table 47. On the LPD, no subject was classified as depressed.

The second control group (Group B) included 10 non-depressed epileptics who were being treated with VPA monotherapy. As mentioned before, VPA is reported not to induce hepatic enzymes. Clinical details of the subjects are shown in Table 47. Using the LPD, no individual was classified as depressed.

6.2.i.b. Special investigations

The post DST cortisol levels for the patient and 2 control groups are presented in Table 48.

TABLE 47: CLINICAL DETAILS OF EST PATIENTS AND CONTROLS

	Patients (N=15)	Control Group A (N=14)	Control Group B (N=10)
	Depressed Epileptics	Non-Depressed Epileptics on Polytherapy	Non-Depressed Epileptics on VPA
Sex:			
Male	4	12	2
Female	11	2	8
Age In Years:			
Range	18 - 65	25 - 51	17 - 47
Mean	39.7	37.6	29.8
SD	14.5	9.6	9.6
Age Of Onset Of Epilepsy:			
Range	4 - 33	1 - 26	3 - 37
Mean	15.1	10.9	18.5
SD	7.9	6.7	10.4
Duration Of Epilepsy:			
Range	4 - 49	11 - 54	4 - 17
Mean	24.6	26.7	11.3
SD	15.3	11.5	4.7
Seizure Type:			
Primary Generalised	1	2	6
Secondarily Generalised	2	6	1
Partial Complex	7	1	2
Partial Complex Secondarily Generalised	5	4	0
Partial Simple	0	0	1
Unclassifiable	0	1	0
EEG Abnormality:			
Normal	1	1	1
Generalised Diffuse	6	9	7
Left Temporal	2	2	2
Right Temporal	3	0	0
Focal Other	1	1	0
Non-Specific	2	1	0
LPD Classification:			
Endogenous Depression	6	0	0
Non-Endogenous Depression	4	0	0
Non-Depressed	3	14	10
LPD-D Score:			
Range	6 - 17	1 - 9	1 - 12
Mean	12.7	4.4	5.8
SD	3.2	2.3	3.3
BDI Score:			
Range	13 - 39	0 - 22	0 - 29
Mean	24.5	6.8	10.0
SD	6.9	7.3	10.3

TABLE 48: POST DST CORTISOL LEVELS

Post DST Cortisol (ng/ml)	Patients	Control Group A	Control Group B
Range	65-285	91-250	14-390
Mean	143.9	173.1	92.3
SD	60.2	48.4	110.2

6.2.ii. Analysis of data

It can be seen from Table 48 that the patients on VPA monotherapy have lower post DST cortisol levels than either of the other 2 groups. Using the Kruskal-Wallis 1-way ANOVA this is significant (KW Chi^2 = 11.9; p = .003). Moreover, when the 3 patients who suppressed cortisol post DST (in the VPA monotherapy group) are excluded from the analysis, the lower post DST cortisol values for non-suppressors on VPA monotherapy remain significant (KW Chi^2 = 7.0; p = .03).

All of the 15 depressed epileptics and 14 non-depressed epileptics (Group A) who were on anticonvulsants which induce hepatic enzymes failed to suppress cortisol after the DST. Three of the 10 non-depressed epileptics on VPA monotherapy suppressed cortisol post the DST while 7 did not. It can be seen from Table 49 that this is statistically signficant.

TABLE 49: RESULTS OF DST

	Number of patients failing to suppress cortisol	Number of cortisol suppressors	Total
Patients on various hepatic enzyme inducing anticonvulsants	29	0	29
Patients on VPA monotherapy	7	3	10
Total	36	3	39

Fishers Exact Probability Test p = .013

6.3. The Double Blind Antidepressant Trial and Pharmacokinetic Study

6.3.i. Description of the sample

Forty-two patients fulfilled the criteria for entry into the trial. There were 3 who dropped out. The clinical details of the 39 patients who completed the 6 week trial are presented in Appendix 12. Tests of significance showed that fewer patients on amitriptyline than on nomifensine or placebo were classified as endogenously depressed, using the Newcastle diagnostic scale ($Chi^2 = 6.5$; $p = .04$; 2 df) and that less patients on placebo than on either of the drugs had entertained or attempted suicide ($Chi^2 = 6.5$; $p = .04$; 2 df): no other significant differences between the groups were found.

6.3.ii. Analysis of data

Antidepressant response

The mean 21 item HDRS, BDI and STAI-State scores for the patients on amitriptyline, nomifensine and placebo for 6 weeks are shown in Figures 3, 4 and 5. At the beginning of the trial, at week 0, there were no significant differences between any of the scores of the rating scales of the 3 groups.

Considering the HDRS, in all treatment groups there was a significant drop in scores over the 6 weeks ($F_{3,108} = 35.17$; $p < .0001$), but no significant differences between either of the drugs or placebo ($F_{2,36} = .08$; $p = .92$) (see Figure 4).

The mean BDI scores also dropped significantly over the 6 weeks of the trial ($F_{3,108} = 18.31$; $p < .0001$), but no differences were detected between any of the treatment agents ($F_{2,36} = .27$; $p = .77$), (see Figure 5).

The A-State scores also fell significantly over the 6 weeks ($F_{3,90} = 6.50$; $p < .001$), but no differences were found between either drug or placebo ($F_{2,30} = .11$; $p = .99$), (see Figure 6).

In summary, the HDRS, BDI and A-State scores all fell significantly over the 6 week treatment period, but no significant differences between any of the trial drugs emerged. The means and standard deviations for the 21 item HDRS, BDI and A-State throughout the 6 week double blind trial are presented in Appendix 13.

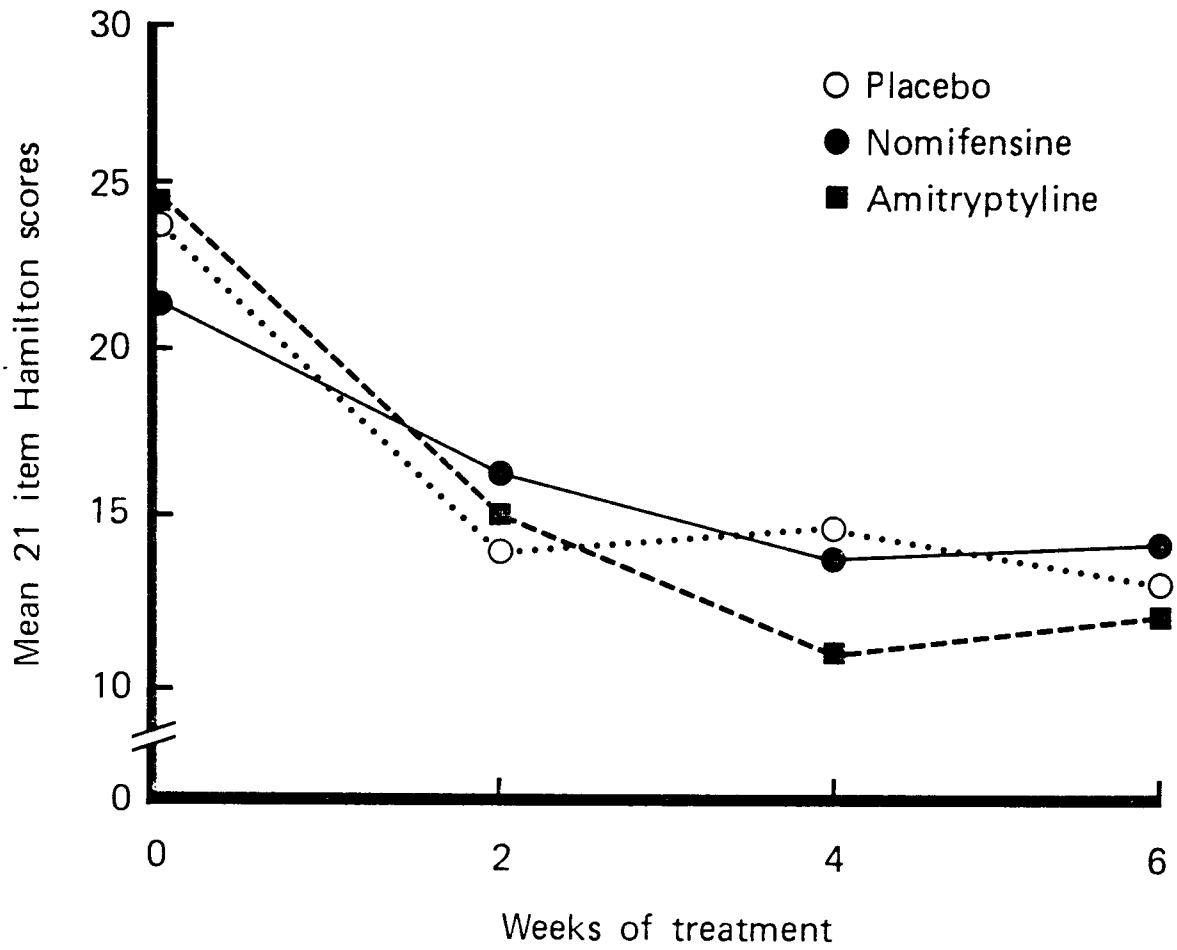

Figure 4

MEAN 21 ITEM HDRS SCORES FOR THE 6 WEEK DOUBLE BLIND TRIAL

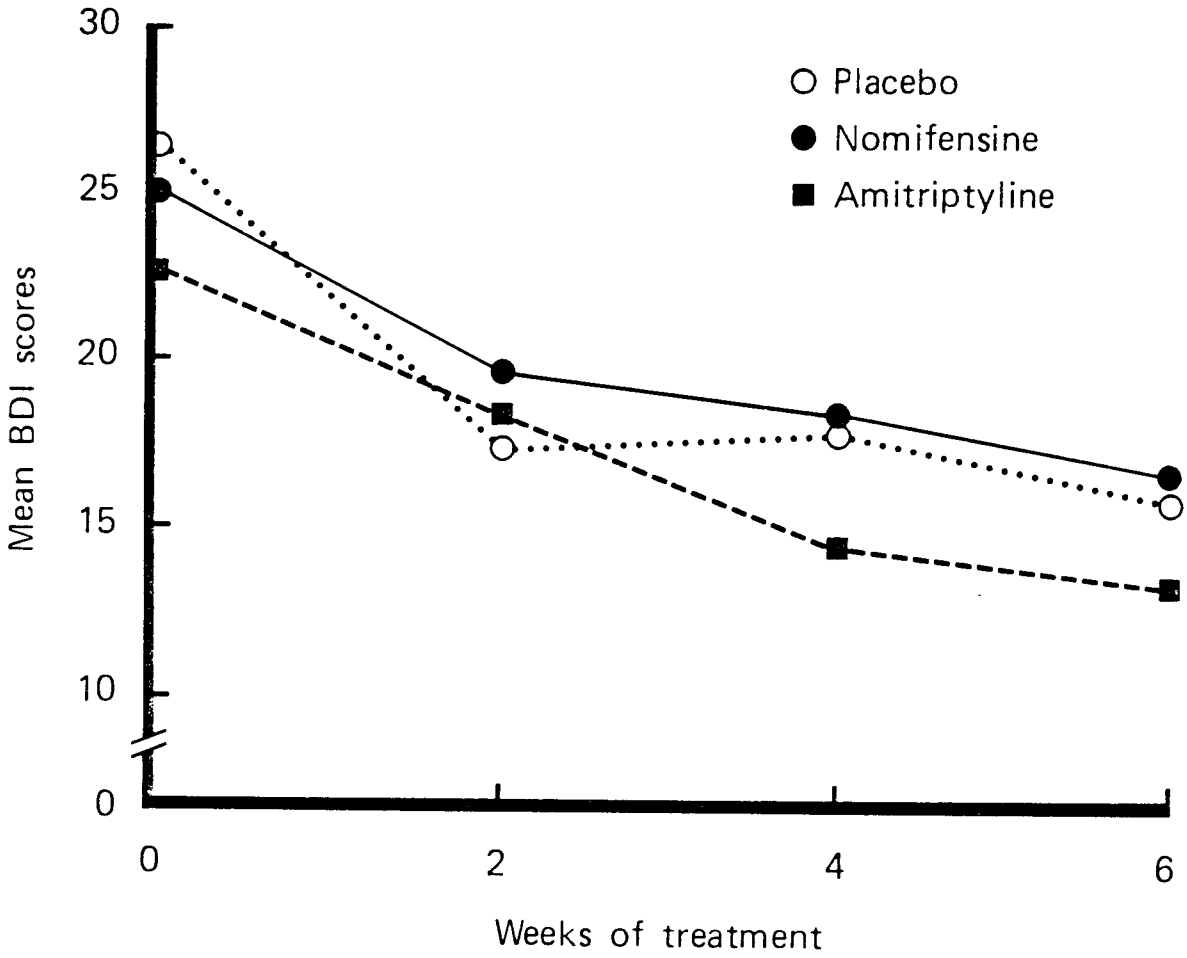

Figure 5

MEAN BDI SCORES FOR THE 6 WEEK DOUBLE BLIND TRIAL.

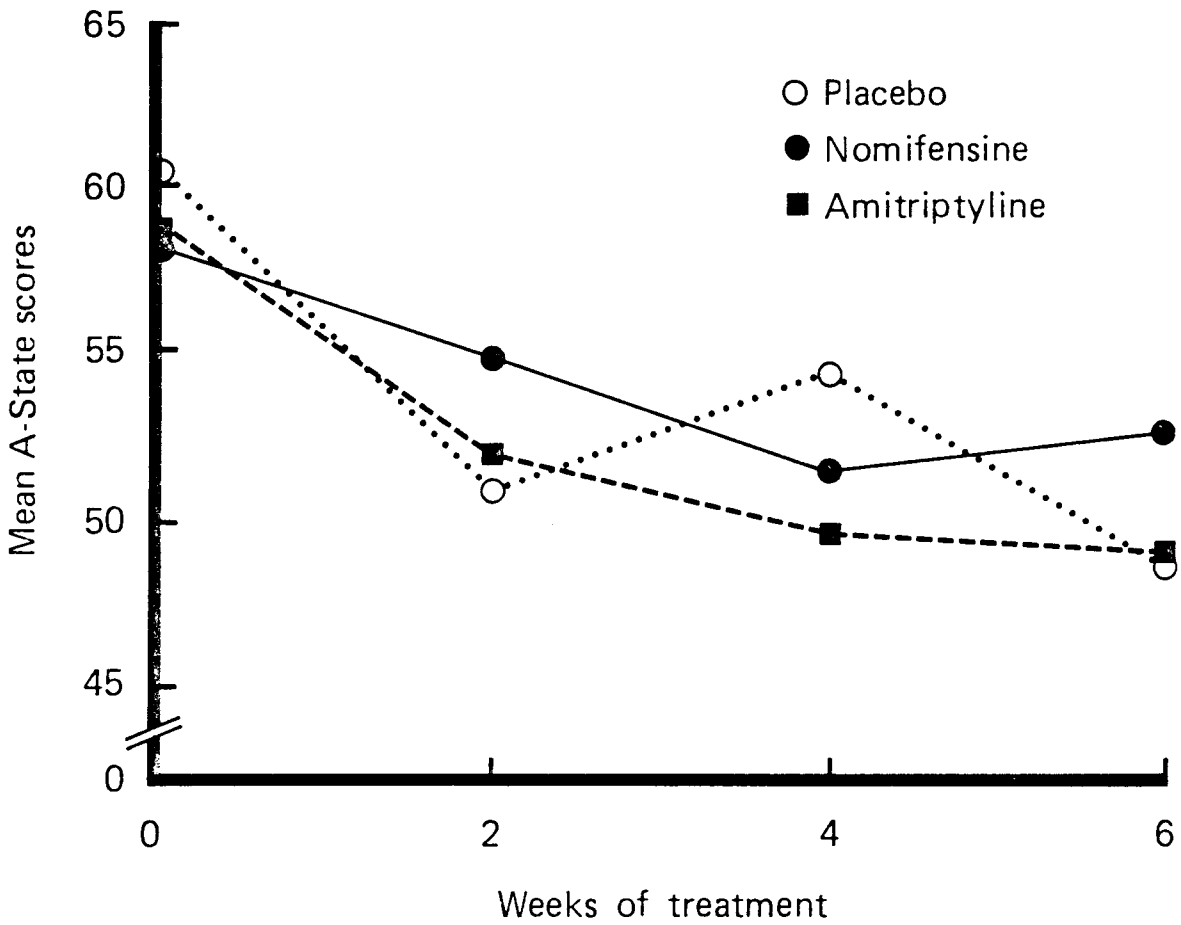

Figure 6

MEAN STAI A-STATE SCORES FOR THE 6 WEEK DOUBLE BLIND TRIAL

Serum antidepressant levels

There were no significant differences in serum amitriptyline levels between weeks 2, 4 and 6 of the double blind trial ($F_{2,16} = .05$; $p = .95$), but the 13.00 hrs levels were significantly lower than the 09.00 hrs levels ($F_{1,8} = 13.76$; $p = .006$). The results were similar for nomifensine, in that the serum levels showed no differences at weeks 2, 4 and 6 ($F_{2,12} = 2.10$; $p = .16$); the 13.00 hrs levels were significantly lower than the 09.00 hrs levels ($F_{1,6} = 61.27$; $p = .0002$).

Serum antidepressant levels and clinical response

Using the Spearman correlation coefficient, no significant relationships between serum amitriptyline or nomifensine levels and the clinical state at 6 weeks, measured by the BDI and the 21 item HDRS were found.

Clinical response was measured by subtracting the score at week 6 from that at week 0 on both the BDI and HDRS.

Using the Spearman correlation coefficient, no significant associations were found between nomifensine levels and clinical response, on either of the rating scales.

However, significant and negative correlations emerged between clinical response judged by the HDRS and amitriptyline levels at both 09.00 hrs ($r_s = -.53$; $p = .04$) and 13.00 hrs ($r_s = -.51$; $p = .05$). In addition, significant and negative correlations between clinical response assessed by the BDI and serum amitriptyline levels at both 09.00 hrs ($r_s = -.57$; $p = .03$) and 13.00 hrs ($r_s = -.59$; $p = .02$) were found.

Serum anticonvulsant levels

Table 50 presents the results of the statistical analysis of the relationship between the serum anticonvulsant levels and the trial drugs (amitriptyline, nomifensine and placebo), time (weeks 2 to 6) and hour (09.00 hrs versus 13.00 hrs).

TABLE 50: RESULTS OF DRUG, WEEK AND HOUR EFFECTS ON ANTICONVULSANT LEVELS

Anticonvulsant	Trial Drug Effect	Week Effect	Hour Effect
PB	$F_{2,9} = .48$; $p = .63$	$F_{2,18} = .11$; $p = .89$	$F_{1,9} = .10$; $p = .76$
DPH	$F_{2,23} = .15$; $p = .86$	$F_{2,46} = .76$; $p = .47$	$F_{1,23} = 6.95$; $p = .014^{*}$
PR	$F_{1,5} = .09$; $p = .78$	$F_{2,10} = 1.67$; $p = .24$	$F_{1,5} = 41.86$; $p = .001^{*}$
CBZ	$F_{2,12} = 1.02$; $p = .39$	$F_{2,24} = .24$ $p = .79$	$F_{1,12} = 23.57$; $p = .0004^{*}$

* = significant

In summary, there were no significant differences between any of the serum anticonvulsant levels of the patients on amitritpyline, nomifensine or placebo. No differences of anticonvulsant levels were noted between weeks 2 to 6. However, there were significant hour effects for DPH, PR and CBZ, the 13.00 hrs serum anticonvulsant level being significantly lower than the 09.00 hrs level in all cases. No such differences were noted for PB. The numbers of patients on VPA and ethosuximide were too small for meaningful statistical analysis.

The serum anticonvulsant levels for the patients on anticonvulsant monotherapy and the change with the introduction of the antidepressants or placebo are presented in Appendix 14, and will be discussed in the 12 week study section.

Relationship between serum antidepressant and anticonvulsant levels

Using the Spearman correlation coefficient, no significant associations between anticonvulsant and antidepressant levels were found. However, as the numbers of patients on any particular combination of anticonvulsant and antidepressant were small, ranging from 1 to 9, the results should be viewed with caution, and no definite conclusions drawn.

Seizure frequency

Given the large variation in fit frequencies, the small numbers of patients and fits, and patients who could not remember the number of seizures they had, it was decided to look at whether the fit frequency had increased or decreased during the trial. The number of seizures for each patient who reported a definite fit frequency were counted. The patients were placed into 2 groups, those who had increased and decreased amounts of seizures on the trial drug.

From Table 51, it can be seen that there was no statistical difference between placebo, nomifensine or amitriptyline with regard to an increased or decreased seizure frequency.

Of interest is one patient who had had fairly regular seizures, but after being placed on nomifensine, at 18 month follow-up, reported being seizure free. In addition, it should be noted that one patient withdrew from the trial because of an unacceptable increase in fit frequency; the patient was on amitriptyline.

TABLE 51: SEIZURE CHANGE IN 6 WEEK DOUBLE BLIND TRIAL

Trial Drug	Seizure Increase	Seizure Decrease	Total	
Placebo	7	1	8	
Amitriptyline	6	2	8	$p > .05$
Total	13	3	16	
Placebo	7	1	8	
Nomifensine	5	3	8	$p > .05$
Total	12	4	16	
Amitriptyline	6	2	8	
Nomifensine	5	3	8	$p > .05$
Total	11	5	16	

Fisher Exact Probability Test of Significance

Side effects

The majority of patients reported side effects at week 0 before the start of the trial. The individual number of patients reporting side effects on each of the 3 trial drugs at the beginning and end of the trial are shown in Appendix 15. Throughout the trial patients on placebo reported side effects, although by week 6 there were less patients with side effects than at the beginning of the trial: this was most evident for dry mouth, difficulty with accommodation and palpitations. Less patients on nomifensine also reported side effects at the end of the trial, with special reference to difficulty with accommodation, constipation, dizziness, headache and gastrointestinal symptoms. More patients on amitriptyline had the following side effects at the end of the trial: dry mouth, difficulty with accommodation constipation. The number of patients remained similar or slightly less for the remaining side effects. Of interest is that there were few differences in side effects on the 3 trial drugs, and because of small numbers, the results were not subjected to statistical analysis.

A patient on placebo reported a pruritic rash before the trial; it disappeared during the trial. Another patient on placebo developed a pruritic rash during the trial which was attributed to the trial drug. A patient on placebo withdrew from the trial 3 days after commencing, as she had an asthmatic attack and developed a vaginal cyst, being advised by her general practitioner that the trial drug was probably responsible.

6.3.iii. The 12 week study

Antidepressant response

Those patients on active agents who did not respond at 6 weeks, had their dose of antidepressant doubled to 50mg tid. At 12 weeks, significant differences between the 2 drugs emerged.

TABLE 52: RESPONSE TO THE ANTIDEPRESSANTS OVER 12 WEEKS

	Responders	Non-responders	Total
Nomifensine	11	2	13
Amitriptyline	6	7	13
Total	17	9	26

Fisher's Exact Probability p = .048

Looking at Table 52 it can be seen that over the 12 weeks, significantly more patients responded to nomifensine than to amitriptyline (p = .048).

Comparing the mean scores of the various rating scales at weeks 0 and 12, it can be seen that the means of the 17 and 21 item HDRS dropped significantly more in the nomifensine group when compared with the amitriptyline group: the mean scores of the BDI and STAI-State also decreased more for the patients in the nomifensine group, but failed to reach significance (see Table 53). These results are presented graphically in Figure 7.

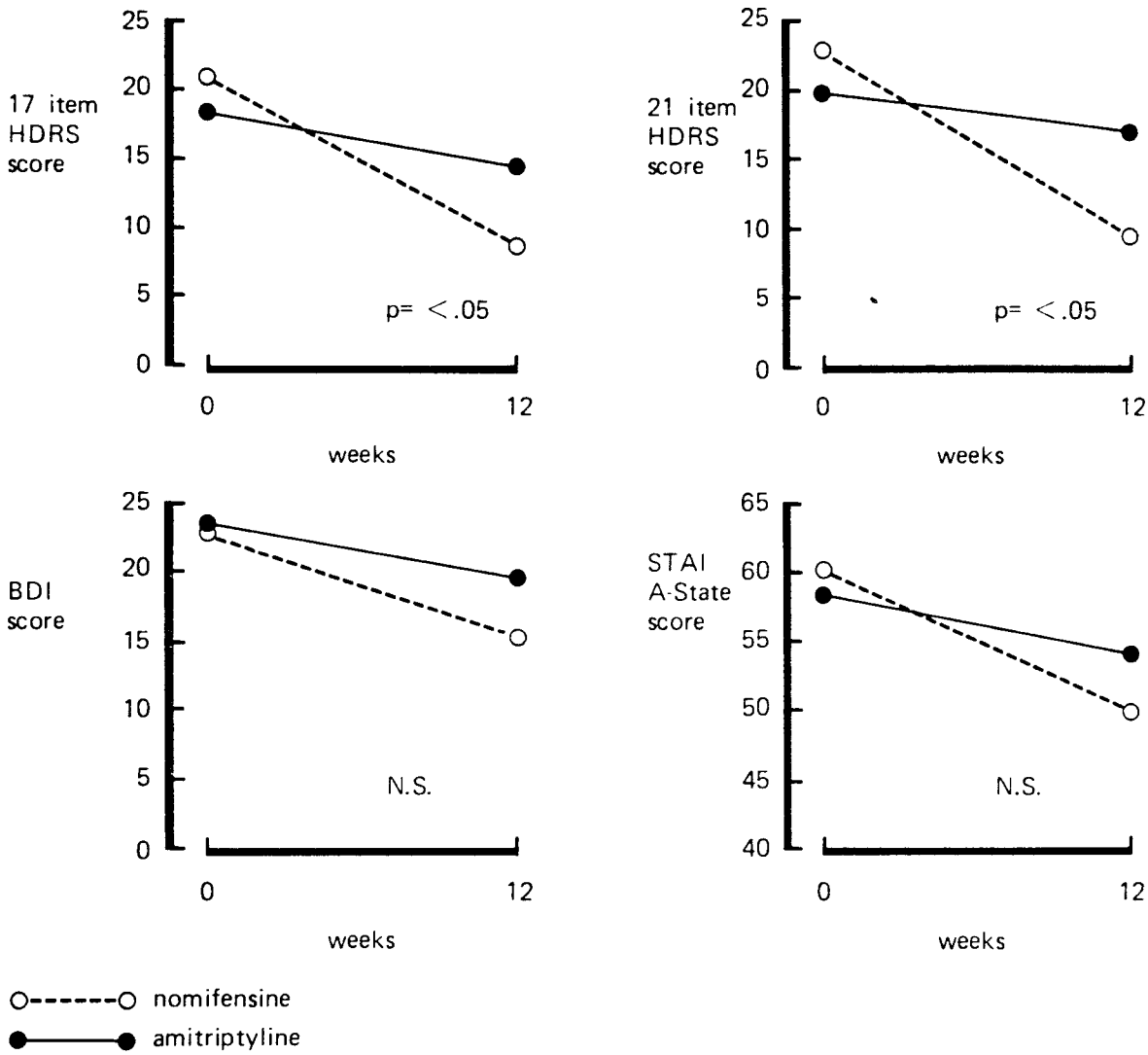

Figure 7

MEAN VALUES OF THE RATING SCALES SHOWING CHANGE IN SEVERITY OF MOOD BETWEEN WEEKS 0 & 12.

TABLE 53: MEANS AND STANDARD DEVIATIONS OF RATING SCALES AT WEEKS 0 AND 12, OF PATIENTS ON NOMIFENSINE AND AMITRIPTYLINE

Rating Scale	Antidepressant	Week 0		Week 12		Significance	
		Mean	SD	Mean	SD	F	P
21 item HDRS	Nomifensine	23.0	5.1	9.5	8.6	$F_{1,11} = 5.2$	$p = .043$
	Amitriptyline	20.0	2.9	17.1	7.0		
17 item HDRS	Nomifensine	21.0	4.9	8.7	7.9	$F_{1,11} = 6.7$	$p = .025$
	Amitriptyline	18.3	2.8	14.7	5.8		
BDI	Nomifensine	23.0	9.7	15.5	16.3	$F_{1,11} = .20$	$p = .662$
	Amitriptyline	23.6	11.4	19.9	12.6		
STAI-State	Nomifensine	60.2	13.8	50.0	19.1	$F_{1,10} = .83$	$p = .384$
	Amitriptyline	58.5	7.4	54.5	11.7		

Serum antidepressant levels

The serum antidepressant levels and mean values for weeks 2 to 6 and 8 to 12 for individual patients are shown in Appendices 16 and 17.

The samples of 2 patients (one on amitriptyline and one on nomifensine) were accidentally destroyed before analysis. Most of the missing values noted in the 2 Appendices were due to sample bottles breaking during freezing, except patient 8 who admitted non-compliance, and patient 38 who was unable to attend 3 sessions.

The effect of doubling the dose of the antidepressants on serum antidepressant levels

The serum amitriptyline and nomifensine levels and mean values for individual patients in the 12 week study are shown in Appendices 16 and 17.

It can be seen that the amitriptyline levels increased markedly at both 09.00 hrs and 13.00 hrs when the amitriptyline dose was doubled, that is between 8 and 12 weeks. This was significant at both 09.00 hrs ($t_5 = 7.15$; $p < .001$) and 13.00 hrs ($t_5 = 4.62$; $p = < .01$).

The increased levels of nomifensine (only calculated on 4 patients as one admitted non-compliance) when the dose was doubled are significant at 09.00 hrs ($t_3 = 4.24$; $p = < .05$), but were not significant at 13.00 hrs ($t_3 = .6$; $p > .05$).

The means and standard deviations of serum antidepressant levels for the 6 patients on amitriptyline and 4 patients on nomifensine at 09.00 hrs and 13.00 hrs between weeks 2 and 6, and 8 and 12 are presented in Table 54.

TABLE 54: MEAN SERUM ANTIDEPRESSANT LEVELS BETWEEN WEEKS 2 AND 6, AND 8 AND 12 (ng/ml)

Antidepressant	Week	Time			
		09.00 hrs		13.00 hrs	
		Mean	SD	Mean	SD
Amitriptyline	2-6	64.7	25.5	44.0	20.1
	8-12	138.2	44.0	101.5	44.6
Nomifensine	2-6	362.5	80.1	215.0	191.1
	8-12	774.8	187.0	468.8	680.1

In conclusion, doubling the dose of amitriptyline significantly increases amitriptyline levels at both 09.00 hrs and 13.00 hrs. Doubling the nomifensine dose produced significantly higher levels at 09.00 hrs but failed to do so at 13.00 hrs.

The relationship between serum antidepressant and anticonvulsant levels

These data were not analysed statistically because of small numbers.

Serum anticonvulsant levels

The serum anticonvulsant levels for those patients on anticonvulsant monotherapy over the course of the trial are shown in Appendix 14.

Four patients on DPH and nomifensine had slight but inconsistent DPH changes. Two patients on DPH and amitriptyline showed an overall slight increase in DPH levels. Inconsistent DPH changes occurred in the one patient on DPH and placebo.

One patient on CBZ and nomifensine showed a rise in CBZ. Two patients on CBZ and amitriptyline and 2 patients on CBZ and placebo showed slight but inconsistent changes in CBZ levels.

One patient on VPA and nomifensine showed marked increases of VPA levels. A second patient on VPA and nomifensine exhibited a moderate increase of VPA at 09.00 hrs and a slight decrease at 13.00 hrs.

CHAPTER 7

DISCUSSION

CHAPTER 7

DISCUSSION

7.1. The Phenomenology of Depression in Patients with Epilepsy

7.1.i. Sources of error

7.1.i.a. Collection of data

The recruitment of patients and rate of referral to the investigator were dependent primarily on the recognition of a possible depressive illness in patients with epilepsy attending routine neurological clinics. This poses problems, as many patients do not complain of depression, but rather lethargy, tiredness or somatic symptoms, which may well have been attributed to the anticonvulsant drugs. Some clinics are run by junior hospital doctors who may not be sufficiently experienced to recognise a subtle psychiatric disorder, as depression can be. These factors would result in omission of referral and thus reduce the number of possible candidates for the study.

Perris (1966) points out that there is always a risk that on being taken into hospital, a depressive patient may display an atypical picture and therefore receive a different diagnosis.

The reliability of the history given by the patient can be a source of error. In most areas, the error would be one of omission, for example, not remembering dates or symptoms, or not knowing of a family history of epilepsy or psychopathology. The accurate history of seizure frequency poses a problem. Patients were able to report whether they had experienced an increase or decrease in their amount of seizures, or whether the frequency had remained the same prior to the onset of the depression. However, further accuracy of seizure documentation may be questioned. At the Chalfont Centre for epilepsy and for in-patients at NHQS, seizures were recorded by trained personnel, but many attacks are not easily recognisable, particularly those of a minor nature, or nocturnal attacks, and it seems likely that some were missed. Accuracy is much more open to doubt in the out-patient sample, especially where a patient lived alone or spent a large part of the day alone. Moreover, it becomes difficult in this situation for the patient who experiences more than one type of attack to be certain about which type he or she had on a particular occasion, because of the subjective amnesia for the episode itself.

7.1.i.b. Assessment of mood and personality: Criticisms of the criteria and rating scales used

The Research Diagnostic Criteria

There are several criticisms of the RDC. One of the important goals of the RDC was to facilitate the selection of clinically homogeneous groups of patients: to this end the authors claim the criteria were selected in order to minimise 'false positives'. However, it has been pointed out that this may not have been so, since the schema has been reported to distinguish poorly between the affective state of widowed individuals and that of patients with major affective disorders (Klein et al 1980). Klein et al (1980) claim the RDC for major depressive disorder are too broad: "they suffer from failure to require autonomy of depressive mood and pervasive anhedonia as necessary clinical aspects" of major depressive disorder, and consequently include people with a variety of dysphoric states. Nelson et al (1978) obtained false-positive diagnoses using the RDC on 2 groups of patients. Murphy et al (1974), in a report dealing with the validity of the diagnosis of primary affective disorder, suggests that criteria should not be used in a "mere checklist fashion", but that they should be evaluated in relation to a "coherent syndrome". Feinberg et al (1979) pointed out that if the RDC are used in a checklist fashion, a heterogeneous group of patients is identified: alternatively, an investigator could interpret the RDC in the light of his clinical judgement, and so narrow the group of patients. Feinberg et al (1979) point out that one method raises the question of their usefulness, the other, their objectivity. The authors then compared the RDC for major depressive disorder with their own clinical diagnoses in 48 consecutive patients at their clinic, and found that the RDC led to both false-positive and false-negative errors, with 30% of patients classified incorrectly. In the present investigation, the patients, who had already been diagnosed as clinically depressed by physicians, and of a sufficient degree to warrant psychiatric help, had to fulfil the RDC as well as score over 12 on the HDRS, in attempt to minimise false positives.

The Hamilton Depression Rating Scale

Several authors have criticised the HDRS. Bech and Rafaelsen (1980) point out that when Hamilton (1960) introduced his scale, he described some factor analytic results, but gave no information about the scale score distribution. They continue to say that most subsequent investigators of the HDRS have maintained the tradition of factor analysing the scale but have neglected the more basic standardisation methods. Moreover, the number of factors researchers have found has varied from study to study, as has the factor morphology (Hamilton 1960; Michaux et al 1969; Mowbray 1972; Welner 1972). Bech (1981) however notes that the most consistent findings seem to be a unimodal factor of severity and a bimodal factor of typology (retardation versus agitation). Overall and Rhoades (1982), however, subjected a sample of 420 HDRS profile patterns to cluster analysis, which revealed 5 distinct subtypes within the population, namely anxious depression, suicidal depression, somatising depression, vegetative depression and paranoid depression.

Although there are criticisms of the HDRS, it was chosen for the reasons justified earlier, and also because it is the most widely used observer rating scale for depression (Carroll et al 1981b).

The Beck Depression Inventory

The scale has been criticised on the grounds that it does not include items concerning retardation, agitation, loss of insight nor anxiety (Hamilton 1969; Snaith et al 1971). Since the HDRS, which does cover these areas, was also employed, this was not a matter for concern in the present study. Another criticism which has been made by Bech (1981), is that the BDI contains no correction scale to estimate patients' test-taking attitude or response set, and the BDI is clearly subject to voluntary distortion or falsification by the patient if he or she wishes. It is quite possible, therefore, for the patient to decide that he or she is severely depressed (without any norms with which to compare the severity) and mark item 3 in a group each time, without perhaps even reading the statement.

In the BDI, the word "blue" is used in item one. This is directed at an American population, and words such as "low", "down" or "unhappy" might be more appropriate in England. Item 2 is about the future, and people with lower intelligence may find it difficult to abstract to make a choice.

Item 16 concerns sleep, but there is no statement which applies to initial insomnia, and many patients find this item difficult to answer. Item 20 is concerned with hypochondriasis. The first 2 sentences mention physical health and physical complaints, whereas statements 3 and 4 are about how the individual feels. Some patients may not realise that they form a continuum, and may well think that "what/how I feel" relates to mood. This question has therefore been altered in an updated version of the BDI; in addition, Beck and colleagues have revised the question on weight loss which covers the possibility that the person is purposely trying to lose weight by eating less. There are also slight scoring differences (Beck et al 1980).

Most questions of the BDI are arranged in quantitative order, but in some instances, such as the question dealing with sleep, a qualitative element is introduced, which does not exhaust the possible patterns of sleep disturbances expressed by depressed patients.

As with the HDRS, the BDI is a widely used rating scale and in this investigation was used to complement the HDRS. In addition, its primarily cognitive structure was thought appropriate for patients with somatic disease.

The LPD Questionnaire

Several criticisms can be made about the LPD. In the Pilowsky and Spalding (1972) paper, one table shows a depression score of 10 as the cut off point between patients who are depressed (both endogenous and non-endogenous) and those who are not depressed; but, another table in the same paper is misleading, as it gives mean scores for neurosis and psychosis with depression as 10.5 and 10.8 respectively.

There are additional criticisms of the scale which may lessen its use in patients with a chronic illness, such as epilepsy, in terms of the questions asked. For example, question 19, "Do you think that you will get better?", can clearly be misinterpreted by patients with epilepsy, and this could also apply to question 43.

Three questions, namely 5, 12, and 51, relate to psychomotor and cognitive slowing, and this may be an effect of chronic anticonvulsant ingestion rather than indicative of a depressive illness.

A possible reason why not many criticisms of the LPD are found in the literature, is because it is not very widely used. One major drawback in this research was the fairly long and complicated scoring method compared with the HDRS and the BDI.

General criticisms

Both the BDI and the LPD can be criticised when dealing with a population of patients who have epilepsy, as the general pessimism and gloom may be a reflection of a chronic illness and, in some cases, institutionalisation, rather than of a depressive illness.

Criticisms can be made against all 3 scales measuring severity of mood with regard the items on sleep disturbance, since all assume insomnia, and none hypersomnia, which may occur in patients with depression. Similarly, loss of weight and appetite are assumed, and again, some depressed patients increase their appetite and weight.

There have been several reports mentioned in Chapter 2, suggesting that people with epilepsy have a low sexual drive. Items on all 3 scales deal with loss of libido, and may therefore not be of value in assessing decreased sexual drive as a measure of the severity of their depression.

Really, one of the problems in a study such as this, is the lack of an effective rating scale for the assessment of depression in neurological illness. In view of the growing importance of this field, such a scale could usefully be developed.

The Newcastle Diagnostic Scale

The Newcastle Diagnostic Scale has a limited use, as it can only be used for classifying the type of depression, in patients already diagnosed as having a depressive illness.

Although acceptable definitions of "adequate personality", "no adequate psychogenesis" and "distinct quality" are stated (see Appendix 6), there is obviously room for observer bias.

Weight loss in excess of 7 pounds is another item of the scale; some patients put on weight with a depressive illness, as has already been mentioned.

A previous episode of depression is an item which is open to criticism, as an individual may be having the first of many recurrent unipolar endogenous depressions.

Lastly, the presence of anxiety is weighted negatively: as was pointed out earlier, most clinicians today accept anxiety as part of a depressive illness, be it endogenous or non-endogenous. In the present project, 12 patients (18%) had a Newcastle score of +5 and were therefore classified as non-endogenous, simply because of the subtraction of one point (because of the presence of anxiety) from a score of 6, which would otherwise have rendered them as endogenous.

The State Trait Anxiety Inventory

Several criticisms have been made with regard to various aspects of the STAI. Some workers found that the A-Trait levels decreased from late pregnancy to the post partum period (Astbury 1980), after treatment with ECT (Newmark 1972), after treatment with TCAs (Mathew et al 1982), after psychotherapeutic intervention (Newmark 1974) and after "kind firmness attitude" therapy (Wadsworth et al 1975). Kendall et al (1976) found the A-Trait to be reliable when repeated administrations were in one situation, but different when the inventory was endorsed in another situation. In the present study, the scales were always completed in similar situations ie. at the special trial clinic, to obviate any situational differences.

Investigators subjected the items of the STAI to factor analysis, and instead of the 2 which would have been anticipated in view of the theoretical State-Trait distinction, some found one (Barker et al 1976; Wadsworth et al 1976) while others found 3 (Barker et al 1977). Kendall et al (1976) also found 3 factors (one being A-Trait and 2, A-State), but the authors concluded that their findings provided support for the State-Trait anxiety distinction, and for the psychometric differentiation of the STAI. The 3 factors found by Barker et al (1977) were not equivalent to those of Kendall et al (1976).

In addition, there is some debate as to the precise nature of A-Trait and what it entails. There is some evidence that high and low A-Trait persons are not differentially threatened by physical dangers (Katkin 1965; Hodges 1968; Hodges and Spielberger 1966; Spielberger et al 1973; Martinez-Urrutia 1975; Kendall et al 1976). On the other hand, performance

differences of subjects who differ in A-Trait are most often found under conditions of threat of failure, threats to self-esteem, personal adequacy, or ego involvement (Spielberger and Smith 1966; Hodges 1968; Hodges and Spielberger 1969; Rappaport and Katkin 1972; Kendall et al 1976; Waid et al 1978), where greater increases in State anxiety have been found in high-Trait-anxious subjects than in low-Trait-anxious subjects. Criticism also comes from those (Endler and Okada 1975; Endler and Shedletsky 1973; Kendall 1976; Blankstein 1976), who contend that the STAI Trait scale is a unidimensional measure that focusses mainly on interpersonal anxiety, ignoring other dimensions such as physical danger and ambiguous threat anxiety, whereas their work supports the notion that A-Trait is multidimensional. This is broadly the same criticism made by those earlier in the paragraph.

Another criticism is that the A-Trait scale allows the subject to provide his own definitional time span for what "how you generally feel" represents: with such ambiguity of time instructions, selectivity in long-term memory may influence the results (Beutler et al 1977).

Finally, the reasonably high reliability of the A-Trait scale reported by Spielberger et al (1970), has been challenged by Nixon and Steffeck (1977), who found that the longer the time period between test and retesting, the lower the reliability.

Although the established values for psychiatric patients have come from males, it was felt justified in applying these norms to the population of the present study, as it has been shown (Beutler et al 1977) that there are no significant differences in scores of male and female psychiatric patients.

One main advantage that this scale has is the ease of administration, and indeed this was found in the present project.

In this section on criticism of the rating scales, it will be noticed that many more criticisms in the literature have appeared with regard to the STAI, compared to the BDI, LPD, HDRS and Newcastle Diagnostic Scale. A possible explanation of this is that the STAI has been used in a much wider range of cultures, situations, clinical and non-clinical populations, than the 4 mood rating scales, which have been used mainly in clinically depressed populations. The kinds of criticisms therefore posed at the STAI will not have been raised on these other rating scales, because of their more limited application.

The Eysenck Personality Inventory

It has been pointed out (Kendell and Discipio 1968) that the customary definition of personality is the "relatively stable and enduring aspects of an individual's behaviour": however, as will be discussed, when an individual is depressed, they obtain "misleading" scores on the EPI - high N scores and low E scores - which alter with treatment. As one of the aims of this study was to obtain information about the patient when depressed, this criticism, although important, does not apply. In addition, Wooster (1963) was unable to find any personality differences between recovered depressives and matched controls, using several different psychological tests, including the short form of the MPI. Kendell and Discipio (1968) note, too, that the mean age of Eysenck's normals is 27 years, and the male/female ratio high: E and N scores both tend to fall with age, and women tend to score higher on N and lower on E than men do. In the present study the mean age was 38 years and there were many more females (N = 46) than males (N = 20). These differences in population might have affected scores.

The Hostility and Direction of Hostility Questionnaire

According to the test manual (Caine et al 1967), only "selected paranoids" (paranoids with no history of depressive episodes) are predominantly extrapunitive, whereas Blackburn (1974) also found manics to be extrapunitive. Philip (1968) administered the HDHQ to large groups of normal people and neurotics: he found that the subscale measuring acting out hostility (AH) did not take its expected place alongside criticism of others (CO) and paranoid hostility (PH) in the extrapunitive dimension. The findings of these 2 authors may reflect a flaw in the HDHQ.

In this project, however, it was found to have good internal consistency, correlate in expected directions with other rating scales, be perfectly acceptable to patients and, in addition, it is one of the few rating scales which purport to measure hostility.

The Hysteroid/Obsessiod Questionnaire

This questionnaire can be criticised on the grounds that obsessional traits are not necessarily similar to obsessional symptoms; if that be the case, the question can be raised "What is the use of dividing people into 2 groups by an arbitrary figure?" The results of the HOQ related to only few items of any other of the rating scales or important clinical aspects of the patients: there was a positive correlation between the HOQ score and extraversion of the EPI (r_s = .53; p = .001), which, as discussed earlier is not unexpected. This really raises doubts about the validity of this measurement, and, in retrospect, another questionnaire for obsessionality may have proved more useful, for example the Leyton Obsessional Inventory (Cooper 1970), or its questionnaire form (Snowdon 1980).

General criticisms

In this study much reliance has been given to self-rated questionnaires. A criticism that can be made of all self-rated questionnaires is the patients' inaccurate assessment of the nature or severity of his or her illness. It is well known that an individual's account of his or her symptoms or illness may neither correspond with accounts given by other informants, nor with the clinician's impression at interview (Goldberg 1969). In a paper on obsessionality, for example, Ingram (1961) pointed out that a person regarded by outside observers as extremely tidy, may either agree, rate himself as untidy, or even claim that he does not think tidiness more important than others do.

The use of rating scales should not be seen as an end unto themselves, and must be used in an intelligent and restricted way. They are not diagnostic tools, and in this study, diagnosis was initially clinical and then depended on the RDC. The use of the scales has been to help quantify symptoms and rate progress of patients, and for those ends they have been shown to be satisfactory.

Generally the correspondence of the results of the rating scales in this study to others are satisfactory, reflecting their potential value. Clearly more sensitive methods could be developed, and the use of microprocessor technology and automated testing may be one future development (Carr et al 1981).

7.1.ii. Factors affecting results

The sample, resulting from a selective referral to 2 specialist centres, is clearly highly selected, although there is no reason to believe that the depressed epileptics in this population should differ fundamentally from those at other referral centres.

The level of motivation an individual exerts when filling in questionnaires may influence the scores obtained; as all patients agreed willingly to participate, it can be assumed that they were fairly well motivated.

Compliance with respect to the regular and correct ingestion of the patients' anticonvulsants prior to the phenomenology section, when venepunctures for serum anticonvulsant levels were taken, is an important issue in any clinical investigation, and may well affect results. As compliance is important in the other 2 parts of the study, it will be considered in detail at the end of the discussion, in a separate section.

7.1.iii. Comparison of the results of the rating scales with previous research in patients with depression or epilepsy

The Hamilton Depression Rating Scale

Table 55 shows the ranges and means of the HDRS scores in various studies of depression, including the present investigation.

It can be seen from Table 55 that the results of the present study compare favourably with those of the studies on depressed patients, using the 17 item and 21 item HDRS. The depression can be considered from moderate to severe.

Roy (1979) examined a consecutive series of 42 patients with epilepsy, and divided them into 2 groups using the HDRS. There were 23 with depressive symptoms (HDRS score 9 or above), and 19 without (HDRS score below 9). The mean HDRS score for the depressed group was 17.1, a figure lower than that of the present study.

TABLE 55: RANGES AND MEANS OF HDRS SCORES IN VARIOUS DEPRESSION STUDIES INCLUDING THE PRESENT INVESTIGATION

Authors	Date	HDRS	Number of Patients	Description of Depressed Patients	Comments	HDRS Range	HDRS Mean
Le Gassicke et al	1964	17 item	30	Out-patients		11 - 45	27.0
Blashki	1972	17 item	61	General practice			17.4
Burrows et al	1972	17 item	32	In-patients		16 - 38	24.0
Mowbray	1972	17 item	347	In-patients			19.4
Carroll et al	1973b	17 item	24	In-patients			29.5
			18	Day patients			23.7
			25	General practice			14.7
			67	All patients			22.4
Bailey and Coppen	1976	16 item	42	In-patients		4 - 33	19.2
Knesovich et al	1977	17 item	26	Out-patients	Number of global ratings = N		
					No depression (N=17)		4.5
					Mild depression (N=19)		10.0
					Moderate depression (N=12)		13.5
					Severe depression (N=19)		23.5
Bech et al	1979	17 item	31	In-patients		5 - 34	19.3
Sheehan	1981	21 item	13	In and Out-patients			22.9
Present study	1983	17 item	66	In and Out-patients		12 - 30	19.6
Present study	1983	21 item	66	In and Out-patients		12 - 33	21.9

The Beck Depression Inventory

As mentioned earlier, a cut-off point for depression in a British population has been suggested as 11. Tables 56 and 57 show the ranges and means of BDI scores of various populations, compared with those of the present investigation.

TABLE 56: RANGES OF BDI SCORES FOR VARYING DEGREES OF DEPRESSION

	Kovacs et al (1981) (American)	Salkind (1969) (British)	Present Study Number of Patients in each Group*
No depression	0 - 9	0 - 10	2
Mild depression	10 - 15	11 - 17	12
Moderate depression	16 and above	18 - 23	13
Severe depression		24 and above	39

*Using Salkind's (1969) ranges

TABLE 57: MEAN BDI SCORES FROM VARIOUS POPULATIONS AND THE PRESENT STUDY

Doctors Rating	No Depression		Mild Depression		Moderate Depression		Severe Depression	
	N	Mean	N	Mean	N	Mean	N	Mean
English study N = Number of ratings (Metcalfe and Goldman 1965)	32	5.37	44	14.27	24	24.21	20	29.5
English study N = Number of patients (Johnson and Heather 1974)	0	-	37	15.9	36	23.7	0	-
American study N = Number of patients (Beck et al 1961)	115	10.9	127	18.7	134	25.4	33	30.0
Present study N = Number of patients					66	24.9		

It can be seen from Tables 56 and 57 that the majority of the patients in this study, 39 (59%), can be considered as severely depressed, although the mean for the group as a whole falls into the category of moderate depression.

In the present study, the BDI correlated significantly with both the 17 item and 21 item HDRS (see Table 31), which is in agreement with the majority of the investigations using both rating scales, as discussed in Chapter 5. Although they are significant, the correlations are somewhat lower than those given by others, which may be a reflection of the neurological illness, increasing scores on somatic items. Again this reflects the need for better methods in the evaluation of depression of these patients.

Another possible reason is that the flavouring of the depression seen in patients with epilepsy may be somewhat different, for example due to the ingestion of anticonvulsant drugs, a further reason to consider the development of special rating scales to assess the severity of depression in neurological disease.

Finally, differences may be reflected as various and different correlation coefficients are used in studies, and are not always quoted.

LPD Depression Score

The LPD-D scores of various studies and the present investigation are presented in Table 58.

These results show that patients from the present study are at least as depressed, if not slightly more so, than those in other investigations using the LPD.

Of importance is that the item of feeling a "burden to others" on the LPD questionnaire was experienced by 54 patients (81.8%). It was significantly associated with depressive variables - type, severity and intropunitiveness, but no significant associations with any epilepsy variables emerged.

TABLE 58: MEAN LPD DEPRESSION SCORES OF DEPRESSED PATIENTS AND THOSE IN THE PRESENT STUDY

Author	Year	LPD Classification and Mean LPD-D Score		
		Endogenous	Non-Endogenous	Not Depressed
Pilowsky and Spalding	1972	14.5	14.5	6.5
Levine	1975	12.7	10.6	-
Pilowsky	1979	10.8	9.8	6.8 (female) 9.3 (male)
Present study	1983	14.0	13.0	8.7

In summary, the severity of the depression on all 3 rating scales used was comparable with moderate to severe depressions of studies using non-epileptic depressed patients, but more severe than the depression of Roy's (1979) depressed epileptic population. The latter result could be explained by the fact that Roy's HDRS cut-off score was 9, whereas that of the present study was 12: in addition, the patients in the present investigation had to fulfil the RDC to enter the project.

The Newcastle Diagnostic Scale and LPD Classification

The type of depression was endogenous in 28 patients (42.4%) using the Newcastle scale, and in 25 patients (37.9%) using the LPD. The only other study which classified depressed epileptics was that of Betts (1974), who classed 12 out of 22 depressed epileptics (54.5%) as having endogenous depression. A possible explanation is that all patients in Betts' study were in-patients in psychiatric hospitals, whereas this sample included both in-patients and out-patients. Further, Betts used purely clinical criteria, which were not standardised, such as the RDC or other research criteria.

In the present investigation, there is an interesting discrepancy between those rated as endogenous depression on the Newcastle scale compared with those on the LPD. Since this is the first study to use both of these scales, it is difficult to elaborate on this. However, further studies are clearly indicated, since the impression gained was that the LPD was possibly of greater value, especially in view of the problem of anxiety on the Newcastle scale mentioned above.

The State Trait Anxiety Inventory

Normative data for the STAI have been reported, as have values for various patient populations, and these, together with the results of the present study, are shown in Table 59. It can be seen that the lowest mean A-State score is 34.8 (normal male university students), while the highest is 60.1 (male neurotic depressives), followed by methadone addicts before maintenance injection (mean 59.8) and the depressed epileptics in the present study (mean = 58.5). The lowest mean A-Trait score is 33 (normal female healthy controls), the highest being 57.4 (male neurotic depressives), followed by methadone addicts before maintenance injection (mean = 57.1) and the depressed epileptics in the present investigation (mean = 56.2). Thus, the depressed epileptics have much higher State and Trait anxiety than any normal population, and higher scores than most groups of psychiatric patients. One possible explanation is that the State anxiety might be part of the depressive illness, whereas Trait anxiety might be related to epilepsy variables which will be discussed later.

The Eysenck Personality Inventory

The normative data for the EPI and scores for various patient populations and the present study are shown in Table 60.

The depressed epileptics from the present investigation have one of the highest neuroticism scores and one of the lowest extraversion scores. Several authors using the MPI and EPI (which Eysenck and Eysenck 1975 say are so similar that they are interchangeable with regards N and E scores), have demonstrated that when depression is treated, N scores fall, while E scores rise (Coppen and Metcalfe 1965; Levinson and Meyer 1965; Ingham 1966; Kerr et al 1970; Philip 1971). Kendell and Discipio (1968), using the EPI, showed N scores to fall with treatment of depression (14.0 to 13.6) and E scores to rise (11.4 to 12.3), although the changes were not significant. One of the reasons the depressed epileptics had high N scores is because the EPI is sensitive to depression. This would also complement the findings of Standage and Fenton (1975) who found higher N and lower E scores in a group of psychiatrically impaired epileptics compared with a control group of epileptics from a neurology clinic.

TABLE 59: STAI A-TRAIT AND A-STATE MEANS AND STANDARD DEVIATIONS FOR VARIOUS POPULATION GROUPS AND THE PRESENT STUDY

(Results from Spielberger et al 1970 unless otherwise indicated)

Group	A-Trait			A-State		
	Number	Mean	SD	Number*	Mean	SD
Normal						
Female controls(1)	26	33.0				
Freshmen - male	332	38.1	8.2	334	40.0	7.9
- female	644	38.2	8.2	648	39.4	8.6
Undergraduates - male	253	37.7	9.9		36.4	9.7
- female	231	38.3	9.1		35.1	9.3
Male students(2)	16	34.2			34.8	
Females in labour(3)	27	-	-		44.0	10.4
Migraine sufferers(1)	31	40.0	-		-	-
Total medical and surgical patients (male)	161	41.9	12.7		42.4	13.8
Patients with psychiatric complications	34	44.6	14.1		42.4	15.7
Patients without psychiatric complications	110	41.3	12.6		42.7	13.8
Methadone addicts(4)						
Before maintenance injection	19	57.1	9.4		59.8	10.7
After maintenance injection	19	55.3	7.9		40.6	7.8
Total psychiatric patients (male)	461	46.6	12.4		47.7	13.2
a) Depressive reaction	28	53.4	12.9		54.4	13.0
b) Anxiety reaction	60	48.1	10.7		49.0	11.6
c) Schizophrenia	161	45.7	12.4		45.7	13.4
d) Brain damage	31	44.6	11.2		46.9	13.4
e) Character disorder	22	40.3	13.1		40.5	14.3
Neurotic depressives (male)(2)	16	57.4			60.1	
Psychotic depressives (male)(2)	12	54.0			55.3	
Prison inmates (male)	212	44.6	10.5		46.0	11.0
Present study	59	56.2	10.2		58.5	10.9

1) = Price and Blackwell (1980)
2) = Wadsworth et al (1975)
3) = Ledermann et al (1978)
4) = Teichman (1981)

TABLE 60: EXTRAVERSION AND NEUROTICISM SCORES IN VARIOUS POPULATIONS INCLUDING THE PRESENT STUDY

(From Eysenck and Eysenck 1964)

Group	Age		Extraversion		Neuroticism	
	Mean	SD	Mean	SD	Mean	SD
Normal population	27.5	12.0	12.1	4.4	9.1	4.8
Neurological patients (Locomotor disorders)*	-	-	10.2	-	9.6	-
Neurotic patients						
Anxiety	35.0	10.9	9.5	4.0	15.8	5.1
Obsessional	36.1	10.3	8.7	4.3	15.2	5.3
Hysteric	29.6	11.9	11.7	4.4	15.2	4.4
Mixed neurotic	33.4	12.6	10.0	4.3	14.4	5.5
Psychotic depressive	46.7	16.1	10.7	4.2	13.3	6.3
Epileptics (Neurological clinic)*	36.0	-	10.9	-	9.8	-
Epileptics (Psychiatric clinic)*	26.7	-	11.7	-	12.4	-
Present study	38.1	12.9	9.9	3.8	15.7	4.3

* Ref: Standage and Fenton 1975

The high N scores in this study did not correlate significantly with either age of onset nor duration of epilepsy (see Table 34). The results agree with those of Davies-Eysenck (1950) who showed that a group of epileptic men and women differed significantly from various normal groups on 3 tests of neuroticism, of which one was the MPI: the epileptics had higher neuroticism scores. No correlation between length of illness and degree of neuroticism was found, a result from which the author concluded that epileptics tended to have a stronger neurotic predisposition than non-epileptics, and that the neuroticism in the epileptic is not merely a reaction to the illness.

The Hysteroid/Obsessoid Questionnaire

Table 61 shows the mean HOQ scores of various populations, all patient samples being in-patients. The depressed epileptics from the present study have a mean score in the obsessoid range. Only 4 groups of depressed patients had lower (ie. more obsessoid scores), whilst the other 10 groups had higher (ie. more hysteroid) scores.

TABLE 61: HOQ SCORES OF VARIOUS SAMPLES AND PRESENT STUDY

(From Caine and Hope 1967 except where otherwise indicated)

	N	Mean	SD
Normals			
Female general hospital patients (Vinoda 1964)	50	23.3	5.1
Females (Essex)	69	24.0	5.5
Males (Essex)	54	24.0	5.9
Females (Aberdeen)	33	23.5	5.8
Males (Aberdeen)	32	23.7	5.5
Neurotics			
West Essex	93	21.8	6.3
East Essex	60	21.9	5.9
Edinburgh	37	20.5	5.6
Neurotic depressives (Mayo 1967)	14	18.4	5.8
Psychotics			
Melancholics (Group A)	20	18.2	5.6
Melancholics (Group B)	20	18.1	6.0
Melancholics (Mayo 1967)	8	18.3	2.9
Females (Vinoda 1964)	50	21.3	5.2
Psychiatric controls (Vinoda 1964)	50	21.4	4.9
Present study	66	19.6	5.4

In the present study the HOQ score was significantly correlated with the E score of the EPI (r_s = .53; p = .001) which is in agreement with Caine and Hope (1964), who found a significant correlation (r = .70) between the HOQ score and the E score of the MPI.

In the present study, patients who had suicidal ideation or attempts had significantly lower, ie. more obsessoid scores (u = 701; p = .04). These results are in accord with other studies employing the HOQ, presented in Table 62.

TABLE 62: STUDIES USING THE HOQ IN SUBJECTS WHO HAVE ATTEMPTED SUICIDE

(From Goldney 1981)

Authors	Year	Subjects	Results
Vinoda	1966	Attempted suicide patients General psychiatric patients Normal controls	No significant differences, but a trend for suicidal patients and psychiatric controls to obtain more obsessoid scores.
Murthy	1969	Serious attempters Non-serious attempters	Significantly more of the non-serious group scored in the hysteroid range.
Eastwood et al	1972	Attempted suicide patients	"Both men and women have mean scores in the direction of obsessoid personality".
Goldney	1981	Young women who attempted suicide Normal controls	Mean score of attempted suicide group in obsessoid range (20.26) and lower than the control group. Among subjects who had attempted suicide, there was a trend for the high lethality group to have more obsessoid scores.

Obsessionality

Obsessional traits were measured on the HOQ, while obsessional symptoms were assessed using the 21 item HDRS. No significant associations were found between obsessionality on either rating scale and clinical seizure type, site of a focal lesion or EEG abnormality.

These findings are in contrast to those authors who report an association between obsessionalism and TLE patients (Blumer 1975; Waxman and Geschwind 1975; Bear and Fedio 1977). These reports, though, are clinical, and Bear and Fedio (1977) examined only patients with TLE, and not those with other forms of epilepsy. However, in a more recent study (Bear et al 1982), using the Bear-Fedio scale, obsessionality was observed equally as frequently in generalised and temporal lobe epileptic groups.

The Hostility and Direction of Hostility Questionnaire

Table 63 shows the mean HDHQ scores of various populations and patients in the present study. The patients "Neurotic A" were more neurotic than "Neurotic B".

It can be seen that the most hostile group were depressed epileptics (Roy 1979), with a mean hostility score of 26.2. These were followed by non-paranoid schizophrenics, melancholics and the depressed epileptics of this investigation, with a mean hostility score of 24.0. Thus, depressed epileptics seem to have high hostility scores when compared to other psychiatric populations. Further, the direction of the hostility is mainly intropunitive with high self-criticism and guilt. In general, depressives are intropunitive (Gottschalk et al 1963; Gershon et al 1968; Fernando 1977; Bennun 1979; Blackburn et al 1979).

The severity of depression as measured by the BDI, the feeling of being a burden to others on the LPD, and the A-State are all significantly associated with intropunitive scores. With regard the type of depression, the more endogenous scores on the Newcastle scale are significantly correlated with intropunitiveness, while the more reactive the depression as judged by the LPD is associated with extrapunitive ratings. Only the 17 item HDRS and A-State scores were significantly correlated with extrapunitive measures, but these correlations were the weakest of all that emerged (see Table 64).

It is possible to summarise by saying that non-depressed epileptics have hostility scores significantly greater than normals, and similar to psychiatric patients. Depressed epileptics have the highest hostility scores. A possible reason for the high intropunitive scores are clearly related to depressive factors. However, it is unclear why this epileptic population should have such high hostility scores. It is nonetheless interesting that there is an extensive literature on aggression in people

TABLE 63: MEAN SCORES OF THE HDHQ IN VARIOUS POPULATIONS AND THE PRESENT STUDY

Population	Number	Author	Year	Mean Scores						
				AH	CO	PH	SC	G	Hostility	Direction
Normals	47	Caine et al	1967	3.6	3.7	0.8	3.7	1.2	13.0	+0.5
Normals	50	Vinoda	1964	4.0	3.0	0.6	3.5	1.7	12.7	+1.3
Normals	240	Philip	1968						15.7	+3.1
Neurotics A	100	Caine et al	1967	4.6	4.0	1.6	6.9	3.2	20.2	+6.7
Neurotics B	69	Caine et al	1967	3.8	3.3	1.0	5.7	2.1	15.8	+5.3
Neurotics	103	Philip	1968						18.0	+6.1
Neurotic depression	14	Mayo	1967	2.4	2.2	0.9	6.2	2.0	13.7	+8.9
Neurotic depression										
Obsessoid	21	Caine et al	1967	4.3	4.0	1.7	6.9	3.2	20.0	+7.1
Hysteroid	9	Caine et al	1967	4.2	4.0	1.3	8.2	3.0	20.8	+9.9
Personality disorder										
Obsessoid	4	Caine et al	1967	5.3	4.0	2.3	6.8	2.8	21.0	+4.8
Hysteroid	5	Caine et al	1967	5.2	4.4	1.0	5.0	2.0	17.6	+1.4
Attempted suicides	50	Vinoda	1964	5.1	4.1	2.2	6.0	3.7	21.1	+4.4
Female psychotic depressives	20	Caine et al	1967	4.4	4.2	2.3	8.0	4.6	23.4	+9.9
Selected psychotic depressives	6	Caine et al	1967	2.2	2.5	1.3	9.8	5.7	21.5	+19.3
Melancholics	8	Mayo	1967	3.6	5.6	2.0	8.6	5.0	25.1	+11.5
Non-paranoid schizophrenics	20	Caine et al	1967	4.8	5.6	3.6	7.5	4.0	25.4	+5.0
Selected paranoids (female)	14	Caine et al	1967	5.9	5.7	4.4	4.8	2.5	23.2	-3.9
Epileptics										
Non-depressed epileptics	33	Cairns	1974						23.0	
Non-depressed epileptics	19	Roy	1979						19.1	
Depressed epileptics	23	Roy	1979						26.2	
Depressed epileptics	36	Present study	1983	5.5	5.7	1.8	7.8	3.4	24.0	+5.9

TABLE 64: RESULTS OF THE PRESENT STUDY - SIGNIFICANT ASSOCIATIONS BETWEEN THE HDHQ AND OTHER RATING SCALES

Other Rating Scales	HDHQ and Subscales					
	Intropunitive		Extrapunitive			Direction of Hostility
	Self Criticism	Guilt	Acting Out Hostility	Paranoid Hostility	Criticism of Others	
BDI	$r_s = .44$ $p = .008$	$r_s = .41$ $p = .01$				
HDRS (17 item)				$r_s = .34$ $p = .05$		
Newcastle	$r_s = .44$ $p = .01$					$r_s = .52$ $p = .002$
LPD E-R Score			$r_s = .47$ $p = .004$			
Burden to others (LPD)	$u = 134$ $p = .01$	$u = 138$ $p = .01$				$u = 138$ $p = .01$
A-State	$r_s = .43$ $p = .01$	$r_s = .48$ $p = .004$			$r_s = .33$ $p = .05$	
A-Trait	$r_s = .52$ $p = .002$	$r_s = .47$ $p = .004$				$r_s = .42$ $p = .01$

BDI	Intropunitive group have higher BDI scores $u = 133$; $p = .04$

with epilepsy (Pincus 1980). Although still open to much debate (Kligman and Goldberg 1975; Hermann and Stevens 1980), one of the persistent issues is whether TLE is more involved in this. In this study, however, no link between hostility and temporal lobe lesions was found, similar to several other data in the literature (Kligman and Goldberg 1975).

Paranoid symptoms

From the HDRS, those patients who were paranoid had significantly earlier ages of onset of epilepsy, but no associations were found with seizure type nor site of a focal lesion. Paranoid symptoms were found not to be associated with either type nor severity of depression.

On the HDHQ patients with abnormal CAT Scans had significantly higher paranoid hostility and criticism of others (both extrapunitive) scores and sum of hostility scores. However, no relationships were found between these scores and the type of epilepsy or site of a focal lesion.

These results are interesting in the light of the study of Hermann et al (1980), who studied 166 patients with TLE and 84 with generalised epilepsy using the MMPI. They found that patients with TLE of adolescent onset had significantly higher mean scores on various items, including Pd (psychopathic deviation), which is one of the scales associated with potential or actual aggression-acting out, and Pa (paranoia).

In contrast, Ounsted and Lindsay (1981) reported that age of onset of seizures was not associated with the development of a paranoid hallucinatory psychosis in later life; factors found to be related to this were male sex, left sided lesion and active seizures.

Depersonalisation

Patients reporting depersonalisation were judged as significantly more depressed on both the 17 and 21 item HDRS, as having more endogenous scores on the Newcastle scale, and higher neuroticism scores on the EPI. On the HDHQ, they were significantly more intropunitive, with higher self-criticism scores and lower criticism of others scores. Depersonalisation in this study is shown therefore to be related significantly to both type and severity of depression.

Depersonalisation was not, however, significantly related to any epilepsy variables, including seizure type and EEG abnormality. This is in contrast to Lishman (1980) who reports that depersonalisation symptoms may be prominent in patients with TLE.

In conclusion, although there are acknowledged problems with the use of rating scales to assess mood and personality, it allows comparison with other data. From this research, the BDI and LPD seemed satisfactory in the assessment of mood, and possibly one reason is that they, especially the BDI, are not loaded heavily with somatic symptoms. While this is of potential relevance in epilepsy, it would be even more so in studies of other neurological disorders, especially Parkinson's disease and multiple sclerosis. In this study the EPI, the STAI State and HDHQ were useful, as they were sensitive to depression and contain no somatic items; the STAI Trait was informative, but interpretation of the results in view of the general controversy as to the precise nature of Trait anxiety, already discussed, is difficult.

7.1.iv. General comments on the results with special reference to previous research in people with epilepsy

Age of onset of epilepsy

In the present investigation, no significant relationships between age of onset of epilepsy nor type nor severity of depression were found.

These results are similar to those of Hermann et al (1980) who used the MMPI to study patients with TLE and generalised epilepsy, and found that item D (Depression) did not vary with age of onset.

The results of both studies are in contrast to those of Dominian et al (1963), who reported that depression was the most common psychiatric problem of late onset epilepsy, although in that study, the depression was clinically evaluated and described. Mignone et al (1970), using the MMPI, found the depression scores of their epileptic population were higher for late onset fits of whatever kind. The study of Mignone et al (1970), however, investigated general psychopathology using a personality rating scale, and their results are reflective of depressive symptoms rather than depressive illness.

It is interesting that in the present study the age of onset correlated significantly with Trait anxiety. A possible explanation is that with early onset epilepsy, the individual may have had adequate time to adapt to the condition, learned to cope with the sequelae of fits, such that the threat of them is no longer anxiety inducing. However, for patients with late onset epilepsy, the occurrence of a socially disruptive illness may be much more traumatic, and increase the individual's Trait anxiety, as a period of adjustment is necessary. However, to speculate further is difficult, especially in view of the controversial nature of Trait anxiety.

Duration of epilepsy

The duration of epilepsy correlated significantly with the severity of depression as measured by the BDI. Duration of epilepsy and the LPD E-R score correlated for endogenicity. However, when corrected for age, the latter ceased to be significant, while the correlation with the BDI remained significant. However, it was only a weak correlation (r_s = .31; p = .012), but it may reflect an explanation that the longer an individual has epilepsy, the more stigmatised, deprived and consequently depressed he or she becomes: the psychosocial aspects of both depression and epilepsy having been discussed fully in Chapters 1 and 2. This suggestion is borne out by the interesting finding that an increase in seizure frequency was significantly associated with high self-criticism and guilt scores on the HDHQ: people with more seizures having more self derogatory symptoms.

As abnormalities of neurotransmitters have been implicated in the pathogenesis of both depression and epilepsy, as reviewed in Chapters 1 and 2, another possible explanation is that the longer an individual has epilepsy with consequent neurochemical changes, the more it may contribute to alteration of a person's biochemical homeostatic mechanisms with resultant increased proneness to develop depressive illness. In this study no biochemical, for example CSF evaluations were carried out, but future investigations may explore links between changes of biochemistry and fluctuations of mood in depressive epileptic patients in detail.

Some authors (Akiskal and McKinney 1975) view depressive illness as a "psychobiological final common pathway" and the culmination of various processes which converge on those areas of the diencephalon that modulate arousal, mood, motivation and psychomotor function: and, indeed, abnormalities of the hypothalamic pituitary axis have been found in both depression and epilepsy as reviewed in the earlier chapters. Akiskal and McKinney (1975)

take the view that the specific form that the depressive illness will take in a given individual depends on the interaction of several factors, a theory which has relevance to this study: 1) Genetic vulnerability - in the present study 34 patients (52.3%) had a family history of psychiatric illnesses, most of which (as discussed in the genetics section) are reported to be associated with depression; 2) Developmental events (and their disruption by epileptic seizures); 3) Psychosocial events (as discussed); 4) Physiological stressors (again, for example, a seizure), which impinge on diencephalic function, and 5) Personality traits - the patients in the present study had much higher Trait anxiety when compared with other populations.

Seizure type

The types of seizure which predominated in the study were complex partial in 20 patients (30.3%) and complex partial, secondarily generalised in 25 patients (37.9%).

No significant associations were found between seizure type, nor severity or type of depression, nor severity of State or Trait anxiety.

As will be discussed under "Previous Past History of Depression", a significant relationship emerged between patients with complex partial seizures and a history of a previous depressive episode; this group of patients may well form a separate subgroup.

Much has been written on increased psychopathology occurring with certain seizure types (see Chapter 2). Apart from the possible subgroup just mentioned, this thesis does not support the notion with regard to depression in epilepsy. However, in spite of the frequency of this clinical problem, as noted, there are few other studies for comparison. These data are broadly in keeping with the work of Williams (1956) and Betts (1981) who do not mention seizure type, but concluded that ictal depression was not related to any part of the brain.

It may be that, while distinct epilepsy variables can be identified in some epileptic patients with psychopathology, for example the schizophreniform psychoses, in depression other factors are more important as discussed above.

Site of a focal lesion

In this investigation there is no support for the laterality notion that right sided dysfunction is associated with affective disorders in people with epilepsy. Not only were there no significant differences between the

EEG assessments of the patients and controls, but when dextrals only were considered, the number of patients with right temporal abnormalities decreased: among the psychotic dextrals, only one patient had a right temporal lobe focus. In fact, for those who had localised abnormalities on their EEGs, in the total patient group, dextral patients only and the control group, there was a bias towards left sided temporal abnormalities.

Possible reasons for the differing results are firstly that in the present study, the depression of patients had to fulfil the RDC and score over 12 on the HDRS, and was therefore strictly defined. Further reasons may be that the other studies employed small numbers (Flor-Henry 1969; Sigal 1976), no control groups (Gregoriadis et al 1971; Sigal 1976; Hara et al 1980), and only reported in abstract form (Gregoriadis et al 1971), with little detail of methods used.

It is of interest that Pritchard et al (1980) investigating the psychological complications of 56 people with TLE reported that psychopathology, whatever the diagnosis, was highest in patients with left temporal lobe discharges (43%), followed by right (32%) and lastly those with bitemporal (27%) discharges, although these differences were not of statistical significance. This preponderance of left temporal lobe discharges is the same as that found in the present study, although Pritchard et al (1980) only had 2 depressed patients in their sample.

Seizure frequency

Twenty-eight patients (43%) reported a decrease in seizure frequency prior to the onset of depression, which agrees with the several authors who reported this, noted in Chapter 3. However, the seizure frequency was not found to be associated significantly with any depression variables (type, severity nor presence of psychosis) nor epilepsy variables (type of epilepsy nor site of focal lesion).

Again this points to a possible subgroup of patients where biological factors may be particularly important. This was discussed by Flor-Henry (1969) who was impressed, in particular, by less frequent seizures (including minor and psychomotor), and a decrease in the number of major generalised seizures associated with the affective component, in his manic-depressive group. In that Flor-Henry's patients all had TLE and psychosis, the findings in this study suggest the situation may be more complex than stated by him.

Anxiety

Both the State and Trait anxiety of the patients in the study were extremely high. The high State anxiety could be specific to the depression seen in epilepsy or, as discussed in Chapter 1, anxiety phenomena are a frequent accompaniment of depressive illness; however, as many studies investigating depression do not use anxiety rating scales, anxiety is not often discussed or quantified.

Betts (1981) considered both State and Trait anxiety in people with epilepsy. He described how many patients become frightened of their attacks, and some develop a "true phobic anxiety state", so that they are panic stricken at the thought of going into a public place lest they have a seizure, and so the patient becomes housebound. He stresses that the problem with such phobic anxiety in people with epilepsy, tends to be self-reinforcing, as the more anxious a person becomes, especially if he overbreathes, the more likely he is to have an attack.

In this study the high State anxiety might well be due to the depressive illness, as it decreased significantly during the 6 week double blind trial.

The high Trait anxiety, however, may be due to epilepsy variables as discussed by Betts (1981). Another possibility is the role of anticonvulsant drugs already mentioned (Thompson 1981).

Suicidal behaviour

Thirty-four patients (51.5%) exhibited suicidal behaviour, which was significantly associated with more severe depression, but no relationships were found between suicidal behaviour and seizure type, site of focus or EEG abnormality. This is in contrast to Barraclough (1981) who reported suicide to be much more common in patients with TLE. However, this is probably a factor of selection, in the sense that patients who had been successful at suicide were obviously not included in the present study.

Previous depressive illness

In the present study 43 patients (65.2%) had a past history of depression, a figure similar to the 61% of patients with previous depressive illnesses in the series of Dominian et al (1963). Moreover, those patients with a previous depressive episode in the present study had significantly higher depressive scores on 2 rating scales. Those with a past history of depression also had significantly higher A-State scores than those who had no previous episodes.

A significant association between patients who had a past history of depression and complex partial seizures was found. Again, these patients may form a subgroup, for whom the biological hypothesis of depression is applicable. The existence of such a subgroup, linked with temporal lobe abnormalities comes from the work of Hancock and Bevilacqua (1971), Rodin et al (1976a) and Dickmen et al (1983). Further evidence for the existence of a subgroup comes from the work of Post et al (1982) who suggest that temporal lobe and limbic dysfunction may occur in affective illness, possibly through a kindling like sensitisation process.

Only 2 patients in the study had bipolar illness, which is in accordance with the literature which highlights the rarity of mania in people with epilepsy.

Psychosis

Thirteen patients (20%) were psychotic, but no associations were found between the presence of psychosis nor seizure type nor site of a focal lesion.

There were, however, significant relationships between the presence of psychosis and the Newcastle classification. Those patients who had endogenous depression were more likely to be psychotic.

The incidence of psychosis in people with epilepsy, and even more so for depressive psychosis is difficult to establish. Fenton (1978) quotes 4 series which looked at this question. In a sample of 27 epileptics attending a neurological clinic 8% had a previous history of psychosis. A survey of 80 successive admissions of patients with epilepsy to the Maudsley (psychiatric) Hospital, 17% had a diagnosis of psychosis. In 2 series of 100 patients treated by temporal lobectomy for intractable temporal lobe epilepsy, the prevalence of psychosis was 12% and 16%. Toone (1981) reviewed several studies based on neurological clinics and the prevalence of psychotics was low, being 4.4%, 2.4% and 2%. Most of these studies have dealt with schizophreniform or paranoid psychoses, and it can be seen that the incidence/prevalence in neurological clinics varies from 2% to 8%, while those from psychiatric centres varies between 12% and 17%.

Toone and Driver (1980) described 15 patients (37%) with affective psychosis out of a sample of 41 psychotic epileptics attending the Maudsley Hospital.

One possible explanation of the high number of psychotics in the present sample and that of Toone and Driver (1980) was that the patients had been referred to psychiatric clinics at specialist centres, where patients with more severe illnesses are referred.

Family history of psychopathology

The finding in the present study of a high family history of psychopathology is in accordance with several authors (Rutter et al 1970; Taylor 1972). The most common disorders were depression and alcoholism and suicide, all of which are more common in families of patients with depression. This suggests a genetic depressive loading for the depressed epileptics, and is in direct contrast to patients with epilepsy and schizophreniform psychoses who characteristically have no family history of schizophrenia (Slater et al 1963). However, the depressed epileptics with a positive family psychiatric history did not have a particular type of depression.

Anticonvulsant drugs and mood

Overall, fairly consistent results emerged between anticonvulsant drugs and mood.

Patients on PB were significantly more depressed judged on 2 rating scales. This is in agreement with Reynolds (1981) who reported improvement in mood and sociability in patients following the reduction or cessation of barbiturate drugs, and Rivinus (1982) in a review article who noted that barbiturates can cause fearfulness, shifts of mood and exacerbations of premorbid psychiatric disorders. Interestingly, in spite of a longstanding clinical impression that PB and depression are linked, this problem has rarely been studied.

It should be noted that a negative correlation emerged between PB dose and depression score on the BDI: there was, however, no significant correlation between PB dose and PB level. This may reflect the problem that some patients were on PB and PR, emphasising some of the difficulties in interpretation of data in this field. Patients on PR had significantly lower scores on the HDRS which is in accord with some of the anecdotal literature with this drug, suggestive of a psychotropic action (Trimble and Richens 1981).

Patients on CBZ were found to be significantly less depressed on the LPD, less guilty and less intropunitive on the HDHQ, and with lower Trait anxiety scores on the STAI. Moreover, there were significant negative correlations between Trait anxiety and CBZ dose, and Trait anxiety and CBZ level. The CBZ dose and CBZ level were significantly correlated. These results are in accord with the literature review in Chapter 3, suggesting a psychotropic action of the drug.

Red blood cell and serum folic acid

There is a large literature, reviewed in Chapters 1 and 2, suggesting low rbc and serum FA in both depression and epilepsy. In a depressed epileptic population, low rbc and serum FA would be expected. This was confirmed by the present study as both rbc and serum FA were highly significantly lower than the control neurological population. However, the low levels were not associated with any depressive variable such as severity or type, nor related to any particular type, dose, or serum level of any particular anticonvulsant. These data are in keeping with Reynolds et al (1971b) and Trimble et al (1980), although in the absence of a non-depressed epileptic control group, little further can be said.

It is of interest that patients with complex partial seizures had significantly lower serum FA than did patients with generalised epilepsy, possible further evidence for this as a biological subgroup. One explanation is that patients with complex partial seizures are more difficult to treat, and thus anticonvulsant factors may be of importance.

7.2. The Dexamethasone Suppression Test

Fifteen depressed epileptics, both with endogenous and non-endogenous depression, all on anticonvulsants which induce hepatic enzymes, failed to suppress cortisol after the DST. A group of 14 non-depressed epileptics, also on anticonvulsants which induce hepatic enzymes, showed the same results. These data are of importance, considering the growing relevance of DST testing in clinical practice. Thus, much of the work (Carroll 1982) has been confined to patients with primary depressive illness, but its value in other patient groups is still far from clear (see Chapter 1). Clearly, in epilepsy, in patients on polytherapy, the test has no value as a biological marker for depression.

However, its use in patients on monotherapy, a growing trend in the management of epilepsy (Reynolds and Shorvon 1981), may be more relevant. Unfortunately, Privitera et al (1982) have shown that patients on CBZ failed to suppress cortisol after the DST, again a suggested mechanism being hepatic enzyme induction.

Since VPA is thought not to induce such enzymes, in this study the effect of the DST has been evaluated in non-depressed epileptic patients on VPA monotherapy. The results show that some patients (30%) suppress cortisol normally as expected, but there are still a high proportion (70%) who fail to suppress. The reasons for this are unclear, but could possibly relate to organic brain damage, which itself may be related to abnormal suppression (Raskind et al 1982; Spar and Gerner 1982; Coppen et al 1983). CAT Scan data was not available on this subgroup, but the possibility that atrophy was somehow related to this finding can be explored in further work.

It is of interest that the post DST cortisol values in the non-suppressing VPA monotherapy patients are significantly lower than those of the other 2 groups. This is supportive of one hypothesis of the mechanism of action of VPA. Thus it is thought to increase GABA in the CNS (Meldrum 1982b), which itself is inhibitory to the control of corticotrophin releasing factor (Bennett and Whitehead 1983), and hence lowers ACTH levels.

In conclusion, to date, the DST does not seem likely to be of value in the assessment of psychopathology in patients with epilepsy.

7.3. The Double Blind Antidepressant Trial and Pharmacokinetic Study

7.3.i. Sources of error

7.3.i.a. Collection of data

Many of the problems discussed in the first section of this chapter apply to the double blind trial, such as recruitment of patients with resultant small numbers assigned to each trial drug group. The reliable reporting of seizure frequency posed a problem, as many patients admitted inaccuracies, and therefore had to be excluded from analysis of data (see Table 48).

7.3.i.b. Methods

Once again, the accurate assessment of mood and especially change of mood is open to criticism. However, all 3 rating scales used to assess mood change, have been widely and satisfactorily employed, as discussed in Chapter 5.

A run-in placebo period of at least 4 weeks to assess not only the seizure frequency prior to the trial, but also to minimise later placebo effects would have been desirable, but was felt to be not ethical. What occurred was reporting of an increase in seizure frequency by many patients on all 3 trial drugs (see Table 48), although this did not reach statistical significance, and was probably the result of the patients' extra care in noting fit frequency, consequent on joining a clinical investigation.

As mentioned, patient 38 was unable to attend 3 sessions, some sample bottles were broken during freezing and the samples of 2 patients were accidentally destroyed before analysis. Although the sampling times were generally as stated in the protocol, ie. 2 and 6 hours after the oral administration of the morning medication (at 09.00 hrs and 13.00 hrs respectively), on a few occasions patients were unavoidably slightly late for appointments.

7.3.ii. Factors affecting results

The highly selected population of well motivated patients might well have partly contributed to the fact that all 3 groups of patients responded significantly at 6 weeks. The fact that the placebo group responded significantly and no differently from the patients taking the other 2 trial drugs merits discussion, which will be at the end of this section.

7.3.iii. Discussion of the results

Serum antidepressant levels

The low levels of amitriptyline (see Appendix 15 for patients who completed the 12 week study) are in accord with reports of low TCA levels in patients receiving barbiturates, as discussed in Chapter 3.

Serum nomifensine levels here (see Appendix 16), are similar to those reported by Bergener et al (1977) in a study of depressed patients taking the drug for 30 days, and Nawishy (1982) in a pilot study of depressed epileptic patients on 25mg tid for one to 12 weeks. This suggests a difference between nomifensine and amitriptyline, namely that nomifensine is less influenced metabolically by the anticonvulsant drugs; this is one possible reason for the better outcome for the depressed epileptic patients on nomifensine following the increased doses.

The finding that neither of the serum antidepressant levels changed between weeks 2, 4 and 6 (ie. show a "week effect") is not unexpected. The patients had been taking antidepressants for 2 weeks before the first blood sampling, and, by then, the steady state would have been reached: steady state is practically achieved after 5 biological half-lives (Levy 1982b). The findings in the present study with regard to amitriptyline levels showing no significant differences between weeks 2, 4 and 6 of the trial is in accordance with another study (Burrows et al 1972).

That the serum nomifensine levels in this study dropped significantly between 09.00 hrs and 13.00 hrs confirms the findings of others (Vereczkey et al 1975; Bailey et al 1977; Dawling et al 1980; McIntyre et al 1982).

Similarly, the serum amitriptyline levels in the present study were significantly lower at 13.00 hrs than 09.00 hrs which is as expected, as peak plasma levels of the TCAs occur within 2 to 4 hours after oral administration (Amsterdam et al 1980), and others (Jørgensen and Staehr 1976) report that serum concentration of amitriptyline steadily decreases with time.

Serum anticonvulsant levels

The finding of no significant differences in serum PB and DPH levels in patients taking amitriptyline, nomifensine or placebo, is in keeping with the data of Nawishy (1982), but in contrast to results of Houghton and Richens (1975) and Perucca and Richens (1977) who reported on 5 and 2 patients respectively as discussed in Chapter 3. The conflicting results may, in part, be due to relatively small numbers of patients reported by others, and individual differences, as indeed, idiosyncratic reactions do occur. In this study although there were small numbers, a possible interaction between VPA and nomifensine emerges, which needs to be further evaluated.

The clinical relevance, however, is that both of these antidepressants could safely be given to patients with depression and epilepsy, without fear of precipitating toxicity, and unless idiosyncratic response is suspected, additional assessment of serum anticonvulsants is not called for.

That the serum anticonvulsants in this study did not show a "week effect" is not unexpected. The patients had been taking anticonvulsants for some time before the trial, so would have reached their steady states. In addition, on long-term anticonvulsant therapy, the drugs would have been maximally induced by the regime, so no further changes would be expected.

With regard to the "hour effect" (ie. the significant lowering of the serum anticonvulsant level at 13.00 hrs when compared to the 09.00 hrs level), the patients on PB showed no such effect, as would be expected because of the long half-life, while those on PR did show an "hour effect" which could possibly be due to its short half-life (see Table 9). Both DPH and CBZ showed an "hour effect", which could be explained by the very different peak times reported for both drugs (Levy 1980; Suria and Killam 1980).

Another explanation for the lower levels of DPH and CBZ at 13.00 hrs, is that by 6 hours of ingestion, there may have been time for changes in hepatic metabolism by PB (Davidson 1982), for those patients on polytherapy.

In reality, this is possibly a statistical and pharmacokinetic effect more than clinically relevant in this study, because looking at Appendix 13 the changes do not seem of clinical importance.

The relationship between serum antidepressant levels and clinical response

In the present study, no significant relationships were found between total nomifensine levels and clinical response. These findings agree with those of Montgomery et al (1980a; 1983).

However, significant and negative correlations emerged between clinical response and total serum amitriptyline levels at both 09.00 hrs and 13.00 hrs.

It is difficult to disentangle the literature on the pharmacokinetics and efficacy of amitriptyline and its metabolite nortriptyline, because conflicting findings with regard to the association between clinical response and serum or plasma levels have been reported. Significant negative correlations between nortriptyline levels and response have been found by Coppen et al (1978) and Montgomery et al (1979), while significant positive correlations have been reported for amitriptyline plus nortriptyline levels and response by Braithwaite et al (1972), Ziegler et al (1976) and Kupfer et al (1977). Others have described a "therapeutic window" with an optimal therapeutic range for amitriptyline plus nortriptyline (Montgomery et al 1979; Montgomery et al 1980b), which is similar to the curvilinear relationship for nortriptyline reported by Åsberg et al (1971) and supported by Gruvstad (1973). Others (Kragh-Sørensen et al 1973b) reported a poor clinical response with plasma levels of nortriptyline above 175ng/ml, which confirms the findings of those mentioned who describe the lack of therapeutic effect of excessive plasma concentrations of nortriptyline. No relationships have been found between response and levels of amitriptyline and nortriptyline together (Amin et al 1978; Liisberg et al 1978) or alone (Burrows et al 1972; 1977; Amin et al 1978; Liisberg et al 1978). Comparisons between the various studies are made difficult by differences in defining clinical response, the duration of treatment and methods of patient selection. Nevertheless, it is interesting that, in the light of the findings of the present study, significant negative correlations have been reported between levels of nortriptyline and response by Coppen et al (1978) and Montgomery et al (1979).

In the present study (see Appendices 15 and 16) there were interpatient variations in steady state antidepressant plasma levels between individuals on the same dose, which can be attributed to genetically determined differences in pharmacokinetics, influence of other drugs especially barbiturates, differences in plasma protein binding, degree of absorption, renal excretion of the TCAs and compliance (Braithwaite et al 1972; Burrows et al 1972).

The antidepressant response at 12 weeks

Nomifensine was significantly superior to amitriptyline at 12 weeks. This may have been a differential drug effect.

An alternative explanation is that on randomisation significantly fewer patients (only one) in the group on amitriptyline were classified as endogenously depressed on the Newcastle diagnostic scale, and the literature indicates that for endogenous depressions biological treatments are preferable (Meyer-Gross et al 1974; Bielski and Friedel 1976).

Another possibility is the relationship that was found between the patients' serum amitriptyline levels and the early clinical response; a significant negative correlation. Authors have described poor clinical response with excessively high levels of amitriptyline plus nortriptyline (Montgomery et al 1979; Montgomery et al 1980b). However, this is unlikely, as no patients have serum levels far in excess of the category of the normally quoted therapeutic range of 80 - 200ng/ml for amitriptyline (see Appendix 16). It is clear that in the early part of the trial, nomifensine levels are more within the expected range (see above), which may have influenced this later response.

The placebo

A placebo was introduced into the double blind antidepressant trial for 2 reasons. Firstly, to test the efficacy of the antidepressant agents, although it was realised from the beginning that small numbers may have presented problems with statistical significance. In retrospect, statistical analysis of the results was possible in spite of this limitation. Secondly, the placebo was used as a control in the pharmacokinetic studies. The patients in the trial were informed that they could be taking a tablet which might have no effect, as in previous double blind studies, telling patients that they might receive placebo did not inhibit the placebo response (Park and Covi 1965).

Patients in the present double blind trial responded significantly to placebo and there was no significant difference between placebo and the active agents. This is not surprising, as placebos are often clinically effective, so much so that Beecher (1955) referred to the "powerful placebo". For these reasons, the placebo and what it entails will be considered in detail.

The "placebo effect" refers to "any effect of medical intervention which cannot be attributed to the specific action of the drug or treatment given" (Honigfeld 1964). The frequency of the placebo effect may vary from 0% to 100% depending upon the definition of the effect, the kind and number of subjects, the indication, and external and internal factors, inter alia (Joyce 1982); however, Beecher's figure of a 35% placebo effect is widely quoted as it was a review of 15 studies, although few of these were in depression.

More specifically, Rogers and Clay (1975) reviewed and subjected to statistical analysis, controlled trials of imipramine and placebo in the treatment of depressive illness. Results showed that imipramine was superior to placebo in patients with endogenous depression who had not been institutionalised (14 studies); in addition, in 2 of the 3 trials in reactive or neurotically depressed patients, imipramine was superior to placebo. However in 13 studies where the authors had not reported the endogenous and reactive grcups separately, but described mixed groups, the results were not significant. Thomson (1982) reviewed 75 double-blind trials using TCAs and placebo. In 59% the TCA was superior to placebo; conversely in roughly 40% placebo was as good as an active agent, which corresponds with the figures of Beecher (1955).

Of more importance, Thomson (1982) demonstrated the differences in results when "inert" placebos (lactose or saline) and "active" placebos (atropine) were employed: there was a significant difference where atropine placebo was given, the advantage of the TCA over placebo being significantly less than when an inert placebo was used. It was suggested that the side effects caused by the atropine amplified the placebo response, or that the atropine had a specific antidepressant effect. In the present study, the placebo was inert.

It is important to realise that physiological changes can take place after the administration of placebos; workers have induced changes in blood eosinophils neutrophils, lymphocytes and lipoproteins following the administration of placebo (Cleghorn et al 1950; Rinzler et al 1953; Tucker 1954).

With regards to this study, and perhaps to the treatment of depression generally, where placebo effects are reported, evaluation of new compounds against placebos should be encouraged.

In the present investigation many patients on placebo reported side effects (see Appendix 15), including a pruritic rash, an asthmatic attack and a vaginal abscess. In addition 7 patients on placebo reported an increase in seizure frequency, while one reported a decrease: these changes were not significantly different from those patients on the 2 active agents. Other authors have also noted an increase in fits in patients with epilepsy being attributed to an active drug in double blind studies, to discover the patients were on placebo (Leder 1970; Ralston et al 1970; Norris and Pratt 1971; Allen et al 1982). Similar severe responses have been reported to have occurred in patients on placebo by Wolf and Pinsky (1954) who described one patient who had an anaphyllactoid reaction, a second who developed epigastric pain, vomiting and diarrhoea and a third who developed a pruritic erythematous maculopapular rash.

Some (Stallone et al 1975) have commented upon the fact that side effects may reveal to the research workers or relatives of patients in a double blind trial what medication the patients were taking, thus allowing bias to interfere with the clinical rating of improvement. In the present study, no patients identified themselves to the investigator as being on placebo.

With regards to the reporting of side effects, patients on placebo and nomifensine reported a slight reduction in side effects from week 0 to week 6, which is in accord with other trials (Mehta et al 1980) as it has been suggested that many "side effects" reported are related to the depression or anxiety rather than to the treatment (Kuhn 1972; Mehta et al 1980).

In the present study the patients on placebo responded significantly by week 6 on both the HDRS and BDI ($p<.0001$) and on the A-State ($p<.001$), but no significant differences between the 3 trial agents emerged. This was unlikely to be due to patient disadvantage on randomisation, as all 3 groups were similar, except that the amitriptyline group contained significantly less patients with endogenous depression, and less patients on placebo had entertained or attempted suicide.

In conclusion:

1) The good placebo response reflects that patients with depression and epilepsy should not immediately be given an antidepressant on their first attendance, and that prescribing should wait until the course becomes clarified.

2) Although significant differences between lower doses of nomifensine and amitriptyline were not apparent, a differential effect appeared with higher doses. In view of the fact that amitriptyline probably provokes seizures more than nomifensine (see Table 16), and that one patient on amitriptyline was excluded from the trial because of seizures, there is a suggestion that nomifensine is safer, and possibly more efficacious in the management of depression in people with epilepsy. However, 50mg tid is a more appropriate dosage than 25mg tid, and an appropriate regime to adopt would be the lower doses for the initial few days of treatment, increasing to 50mg tid over the course of 10 days. This gradual increment in dose is in accordance with clinical practice of building up prescriptions.

7.4. Compliance with Medication

In the present investigation the question of compliance is extremely important, as it could have affected results of all 3 parts of the study. Incorrect anticonvulsant usage could affect the seizure frequency, serum levels and even mood of the patients. In the DST, failure to take the dexamethasone could result in abnormally high cortisol levels. In the double blind trial poor compliance could be a source of error. In addition, much has been written on compliance in patients with epilepsy and those with psychiatric illness. It is therefore felt justified, that the question of compliance is addressed in some detail.

Patient compliance has long been recognised as an integral part of the therapeutic drug strategy for all illnesses. Non-compliance has been observed in the treatment of a wide variety of diseases. A review by Blackwell (1972) of over 50 studies found that complete failure to take medication often occurred in between a quarter and over a half of all patients. That drug defaulting may play a part in distorting the controlled evaluation of drug therapy was first remarked upon by Dixon and associates as long ago as 1957, when they noted that "many chemotherapy trials based on unsupervised oral medication have probably been built on

very unsure foundations". The point has been made subsequently by several authors (Joyce 1962; Porter 1969).

One problem is the fundamental lack of any agreed definition of the non-compliant patient variously and arbitrarily described as one who takes less than roughly 30%, 50% or 90% of his treatment (Corrigan and Strauss 1936; Rickels and Briscoe 1970; Veterans Admin. Study 1967).

In patients with epilepsy the problem of non-compliance was first pointed out by Buchthal et al (1960), who estimated that 50% of ambulant patients complied poorly, and was first systematically investigated by Lund et al (1964) who found a poor compliance rate of 66% in ambulatory patients. One can see from Table 65 that in an epileptic population, non-compliance varies from 38% to 75%, with a mean of 49%. Poor compliance in people with epilepsy has also been noted by other authors (Haerer and Grace 1969; Booker 1972; Gardner Thorpe et al 1972). In patients with epilepsy, Sherwin et al (1973) distinguish 3 main types of non-compliance with drug therapy: 1) Partial or erratic compliance in which serum drug levels occasionally fall below individual therapeutic requirements; 2) Consistent failure to take medication in which cases therapeutic levels are never achieved; 3) Excess consumption of drugs due to attempts at self-treatment which may lead to toxic effects.

Among patients attending psychiatric services, non-compliance ranges from 7% to 77% as can be seen in Table 65, with a mean of 16% for in-patients and 51% for out-patients.

The patients in the double blind trial had 2 diagnoses, namely epilepsy and depression, so, according to Sackett (1976) they would be expected to achieve fairly high compliance rate with appointment attendance, which they did. Some patients missed appointments due to unavoidable external events, such as adverse weather conditions (heavy snowfalls in both winters of the trial) and transport industrial action.

Prior to the investigation, a full review of the literature on compliance was undertaken (see Tables 65 and 66) and an attempt was made to ensure good compliance. In the double blind trial, there was an attempt to increase the compliance of attendance, and correct taking of medication, by employing several of the strategies for increasing compliance as shown in Table 66. These included clear explanation and instructions, written instructions,

telephone reminders and home visits to retrieve non-attenders, establishment of a special trial clinic at frequent (2 weekly) intervals, the provision of free medication, making the patient aware of the physical characteristics of the drug and, when felt necessary, the supervision of medication by nursing staff in hospital or a relative at home. There are several methods of detecting tablet defaulters and in the trial, compliance was recorded by the measurement of serum levels of both the anticonvulsants and antidepressants, taken twice daily at each visit. Looking at Appendices 14 & 16-17, it can be seen that on the whole, patients in the present study were reasonably compliant with medication.

TABLE 65: NON-COMPLIANCE IN VARIOUS PATIENT CATEGORIES

Category	Author	Year	Diagnosis	Number of Patients	In/Out Patients	Failure Rate or Non-Compliance
Normal	Siegel et al	1971	Oral contraception	551	Out	45%
	Afifi et al	1966	Antenatal	483	Out	28%
	Benstead and Theobald	1952	Antenatal	102	Out	33 - 40%
	Bonnar et al	1969	Antenatal	60	Out	32%
Medical Acute	Bergman and Werner	1963	Streptococcal infection	59	Out	56% (initial) 82% (end)
	Kilpatrick	1966	Anaemia	-	Out	30 - 40%
	Mohler et al	1955	Pharyngitis and otitis media	245	Out	34%
	Porter	1969	Infections	48	Out/GP	31%
Medical Chronic	Brook et al	1971	General medical	403	Out	33%
	Heinzelman	1962	Rheumatic fever	284	Out	81%
	Johnston and McDevitt	1978	Cardiovascular	50	GP	46%
	McKenney et al	1973	Cardiovascular	49	Out	35%
	Parkin et al	1976	Cardiovascular	130	Out	51%
	Weintraub et al	1973	Cardiovascular	101	Out	34 - 40%
	Lunz and Austin	1960	Tuberculosis	705	Out	34%
	Dixon et al	1957	Tuberculosis	151	Out	50%
	Joyce	1962	Rheumatoid arthritis	78	OPD	65%
	Vincent	1971	Glaucoma	62	OPD	58%
Epilepsy	Dawson and Jamieson	1971	Epilepsy	30	Both	55%
	Gibberd et al	1970	Epilepsy	-	Out	42%
	Kutt et al	1966	Epilepsy	16	Out	75%
	Sherwin et al	1973	Epilepsy	70	Out	38%
	Wannamaker et al	1980	Epilepsy	30	Out	37%
Psychiatry In-Patients	Forrest et al	1961	General psychiatric	A review	In	5 - 15%
	Hare and Willcox	1967	Schizophrenia and depression	120	In	19%
	Irwin et al	1971	General - closed ward	67	In	7%
			- open ward	19	In	32%
	Neve	1958	General	56	In	11%
Psychiatry Out-Patients	Mason et al	1963	General	48	Out	62%
	Michaux	1961	General	180	Out	55%
	Irwin et al	1971	General	40	Out	35%
	Rickels and Briscoe	1970	Neurotics	301	Out	77%
	Lipman et al	1965	Anxious neurotics	254	Out	47%
	Park and Lipman	1964	Neurotic depression	42	Out	51%
	Willcox et al	1965	Depression and schizophrenia	125	Out	48%
	Hare and Willcox	1967	Depression and schizophrenia	27	Day	37%
	Parkes et al	1962	Schizophrenia	96	Out	44%
	Renton et al	1963	Schizophrenia	124	Out	46%
	Hogarty et al	1973	Schizophrenia	374	Out	55%

TABLE 66: METHODS FOR INCREASING COMPLIANCE WITH MEDICATION

Recognition of the "at risk" patient	Blackwell 1973
Clear explanation and instructions	Parkes et al 1962 Porter 1969 Mazzulo and Lasagna 1972 Blackwell 1973 Smith et al 1979 Maryon-Davis 1981
Simplification of medication schedule	Gibson and O'Hare 1968 Haerer and Grace 1969 Porter 1969 Johnson and Freeman 1972 Blackwell 1973 Smith et al 1979
Counselling	Colcher and Bass 1972 McKenney et al 1973 MacDonald et al 1977 Jackson and Edwards 1981
Provision of diary cards or record book	Gibberd et al 1970 Wandless and Davie 1977 Smith et al 1979 Jackson and Edwards 1981 Maryon-Davis 1981
Serum level monitoring (epilepsy)	Gibberd et al 1970 Dawson and Jamieson 1971 Booker 1972 Sherwin et al 1973 Kutt and Penry 1974
Written instruction	Leistyna and Macawley 1966 Watts 1972 Laher et al 1981 Maryon-Davis 1981
Supervision by relative or neighbour	Parkes et al 1962 Blackwell 1973 Smith et al 1979
Monthly injections instead of oral medication	Feinstein et al 1968 Johnson and Freeman 1972
Once daily dosage: less frequency	Porter 1969 Blackwell 1973
Home visits to retrieve non attenders	Anderson et al 1971 Watts 1972 Finnerty et al 1973
Reducing intervals between clinic visits: That is increasing the frequency of visits	Lund et al 1964 Gibberd et al 1970 Wannamaker et al 1980
Free medication	Bonnar et al 1969 Wannamaker et al 1980
Preference for medication with few side effects	Porter 1969 Blackwell 1973
Fitting the regimen to the patients habits	Mazzulo and Lasagna 1972 Smith et al 1979
Telephone reminders	Kidd and Euphrat 1971
Establishment of a special seizure clinic	Gibberd et al 1970
Patients' awareness of the physical characteristics of the drugs	Mazzulo and Lasagna 1972

CHAPTER 8

SUMMARY OF MAIN FINDINGS

IMPLICATIONS FOR DEPRESSION

IN THE CONTEXT OF

EPILEPSY AND THE FUTURE

CHAPTER 8

SUMMARY OF MAIN FINDINGS, IMPLICATIONS FOR DEPRESSION IN THE CONTEXT OF EPILEPSY AND THE FUTURE

8.1. Summary of Main Findings

Review of the literature suggests that depression is one of the most common psychiatric complications of epilepsy. No studies have investigated, in detail or standardised form, the precise phenomenology of the depression. That the depression is severe has been mentioned, and indeed, suicide is much higher in people with epilepsy, especially TLE. The DST in identifying a clinical type of depression in people with epilepsy has not been evaluated in depressed epileptics. There have been no studies dealing with the treatment of the depression: there is much evidence that many antidepressants can lower the seizure threshold and cause convulsions clinically, and there are few reports of the pharmacokinetic interactions between anticonvulsants and antidepressants.

Parallel review of the literature, moreover, indicated that depression and epilepsy have many factors in common, and that the 2 illnesses in one person would therefore be complex.

Three experiments were therefore designed, and despite the methodological weaknesses in the study, the following answers, to the questions addressed, are felt justified (for numbering of questions see Introduction).

1) The phenomenology of depression in the context of epilepsy was assessed using standardised rating scales. Sixty-six patients qualified to enter the investigation. The depression was endogenous in 28 patients (42.4%) using the Newcastle scale and in 25 patients (37.9%) using the LPD. The severity of the depression was moderate, with the following mean scores: 24.85 (BDI) and 12.73 (LPD)*. The patients had high State anxiety (mean 58.54), neuroticism (mean 15.70) and hostility (mean 23.97) with special reference to the intropunitive measures of self-criticism and guilt. These figures are comparable with studies of those of depressed patients, except for the hostility which is higher. The high State anxiety, neuroticism and intropunitive hostility can be regarded as part of the depressive illness. Thirteen patients were psychotic. Fifty-three patients were classified as obsessoid, with the mean score (19.58) being in the obsessoid range. The Trait anxiety was high (mean 56.19), and was felt probably due to epilepsy variables. The main reason for not solely attributing Trait anxiety to epilepsy variables was two-fold:

* and 21.88 on the 21 item HDRS

firstly, the age of onset of epilepsy correlated significantly with Trait anxiety, and secondly, there does seem to be some controversy as to the exact nature of Trait anxiety. Paranoid symptoms and paranoid hostility were related to early age of onset of epilepsy and abnormal CAT Scans respectively, but not to type of seizure or site of a focal lesion. Obsessional symptoms were not related to type of seizure, site of a focal lesion nor type or severity of depression. Depersonalisaion was related to both type (endogenous) and severity of depression, but neither to seizure type nor site of a focal lesion. Suffice is to say that the severity of depression with its attendant high State anxiety, neuroticism, hostility and feelings of depersonalisation, in people who have high Trait anxiety, is sufficient to warrant treatment.

2) People with different types of epilepsies do not differ in the type of depressive syndrome with which they present. Neither the type of epilepsy, site of a focal lesion (EEG abnormality or CAT Scan abnormality) nor seizure frequency influence the phenomenology of the depression. Few epilepsy variables were found to be significantly related to aspects of depression. The duration of epilepsy correlated significantly with the severity of the depression as measured by the BDI ($p < .05$). A significant association was found between patients who had complex partial seizures and a past history of depression ($p < .05$): in addition, patients with complex partial seizures had significantly lower serum FA ($p < .05$) than did those with generalised epilepsy. Several theories were advanced as to these relationships, and it was suggested that there may be a subgroup of people with complex partial seizures who are more prone to depression. The overall conclusion, however, was that the depression was not influenced by epilepsy variables.

To investigate, in more detail, the question of laterality, (the site/side of a lesion), the EEGs of 66 consecutive age and sex matched epileptics with no history of psychiatric illness were examined. No statistical differences between the EEG abnormalities of patients and controls emerged. Moreover, considering only those who had focal abnormalities on their EEGs, in the total patient group, dextral patients only, and control group, there was a bias towards left temporal abnormalities.

3) A positive history of family psychopathology was found in 34 patients (52.3%). Depression was the most common diagnosis; alcoholism, suicide and "other" psychiatric illness (including psychoses and "nervous breakdowns") were evident. This is suggestive of a genetic predisposition. However, no relationships were found between a positive history of psychiatric illness in the family and any type of depression, nor psychosis.

4) Important findings regarding the anticonvulsants and mood, were that patients receiving PB were significantly more depressed ($p<.05$), while those receiving CBZ were significantly less depressed ($p<.05$) and had significantly lower Trait anxiety ($p<.05$).

5) The rbc FA ($p<.001$) and serum FA ($p<.05$) were significantly lower than that of a control population. However, no significant relationships were found between rbc and serum FA and type or severity of depression, presence of psychosis, nor any epilepsy variables, including the anticonvulsants.

It is concluded that depression in people with epilepsy may well represent the outcome of multiple factors in genetically predisposed individuals. The possibility that a subgroup with a more biological loading is raised.

The second study investigated the usefulness of the DST in identifying certain clinical features in the depressed patient with epilepsy. Due to the hepatic enzyme induction by most anticonvulsants, the DST is of no practical value in depressed epileptics, as the majority are non-suppressors of cortisol post DST. However, what emerged was that a control group of non-depressed epileptics on monotherapy with VPA, which is reported not to induce hepatic enzyme systems, differed significantly in their reaction to the DST ($p<.05$). In addition, the post DST serum cortisol levels for the VPA patients were significantly less ($p<.01$) than depressed epileptics and non-depressed epileptics on anticonvulsants reported to induce hepatic enzymes. It is suggested that VPA interferes with cortisol production via GABA-ergic mechanisms.

The third part dealt with the treatment of the depression and involved a double blind antidepressant trial and a pharmacokinetic study. The questions are answered as follows: (for numbering of questions see the Introduction).

1) Antidepressant drugs and placebo are effective as antidepressants when the former are given in low doses. With higher doses a difference between amitriptyline and nomifensine emerged, in favour of the latter.

2) The antidepressant effect of nomifensine is unrelated to serum antidepressant levels at 6 weeks. There was a significant negative correlation between serum amitriptyline levels at 6 weeks and clinical response.

3) Doubling the dose of both amitriptyline and nomifensine significantly increases serum levels of both.

4) No significant differences were found in the anticonvulsant levels between the patients on nomifensine, amitriptyline or placebo. From this, and looking at the levels of patients on anticonvulsant monotherapy, it was concluded that antidepressant drugs did not significantly alter the level of the anticonvulsants. Although the numbers are small, the interaction between nomifensine and VPA suggests pharmacokinetic interaction, which should be examined further.

5) No relationships between serum antidepressant and serum anticonvulsant levels were found.

6) Given at therapeutic doses, antidepressant drugs do not provoke clinical seizures in patients with epilepsy.

8.2. Suggestions for future research

1) It is suggested that further double blind antidepressant trials be undertaken. The investigation reported here had several shortcomings, discussed above, which it would be desirable to overcome in future projects. Ideally, it should not have a time limit and therefore enable the investigators to collect more subjects. Populations studied need to be more homogeneous with respect to anticonvulsant treatment (ideally they should be on monotherapy) and also type and severity of epilepsy. There could be a run-in period of 4 weeks on placebo, during which fits are accurately documented and a baseline EEG is done. This would provide valuable information about possible fluctuations in these variables and thus lead to a better interpretation of any "post-treatment" changes. The method of seizure documentation should be carefully planned with consideration of type as well as frequency of attacks. Serial EEGs should be done throughout the trial

at weeks 2, 4 and 6, as they may give more indication of what effect the antidepressants are having on the seizure threshold. It may be possible with recent advances in technology to increase the objectivity of the EEG analysis by including computerised assessment of the traces. Serial testing of mood could be done using automated testing and a microcomputer, time saving for medical personnel, patients are reported to have commented favourably on it (Carr et al 1981) and it may well be more accurate. Furthermore, with the more widespread use of such techniques, multi-centre projects would appear more plausible. Inter-centre variability in testing procedures could be minimised by using identical programs. Data could be stored on discs and analysed collectively. This would enable more rapid accumulation of information on similar patients who are on the antidepressants in the trial. Other antidepressants which are still relatively safe (see Table 16) could be used as trial drugs. For example Ojemann et al (1982) have recently reported some clinical anticonvulsant effects for doxepin, but whichever antidepressant is chosen, placebo control should be included. A more thorough investigation of the social circumstances of the patients than employed in this study seems desirable: this could be achieved with the aid of life event questionnaires, which could be usefully employed in further investigations of the relationship between depression and epilepsy. External events can alter the outcome of a trial and, if possible, an in-patient population would control some of these factors. In addition, in hospital, drug-dosage regimens, blood sampling times and other medications (if any) can be carefully controlled.

2) It is suggested that a useful contribution to clinical research would be the development of a rating scale for the evaluation of the severity of a depressive illness in people with neurological disease, which includes epilepsy. The questions would have to exclude somatic items (12, 13, 15 on HDRS, 20 on BDI), those to do with libido (14 on HDRS, 21 on BDI, 23 on LPD), and those querying a bodily illness (15 on HDRS, 43 on LPD). Questions regarding work and interests (7 on HDRS) would have to be worded carefully, as many people with neurological disease are not able to take part in their normal past activities because of their neurological illness. Similarly, questions dealing with middle and delayed insomnia (5, 6 on HDRS) would have to relate to waking up with concomitant subjective dysphoria, rather than to micturate during the night, which many people with neurological disease do. For epilepsy, particularly, questions to do with impaired cognition (5, 12 on LPD) would have to be excluded or reworded, as the symptom may be due to anticonvulsant ingestion and not a depressive illness. In the same

way, signs or symptoms of psychomotor retardation (8 on HDRS), would have to be evaluated carefully, as they could be due to toxicity of anticonvulsant drugs. To be of value, such a scale would have to be tested for reliability and validity, and should be sufficiently short to be given to patients without fatiguing them. Although a self-rated questionnaire is to be preferred, the presence of neurological disability may make observer rated scales more reliable; however, the use of microprocessor technology could be explored in this regard.

3) Further attempts to isolate any group of epileptic patients with a biological vulnerability to depression directly related to their epilepsy could be undertaken. Thus, more extensive phenomenological examination of those with only complex partial seizures may be rewarding, in particular, further attempts to disentangle relationships between seizure frequency and the onset of depressive illness. If larger numbers were available, and this would probably involve a multi-centre study, greater examination of patients with affective psychosis and its relationship to epilepsy variables may be rewarding.

4) In this study the relationship between anticonvulsant drugs and depression has been only partially disentangled. The hints of differences between drugs suggest that further studies of this important area are required. Patients starting monotherapy for the first time would be an ideal group to look for changes of mood during treatment, particularly if monotherapy with different anticonvulsant drugs could be evaluated. The role of polytherapy could be examined further by comparisons of mood changes in patients withdrawing from such treatment onto selected monotherapy.

5) Since the DST appears unhelpful as a biological marker for depression in epilepsy, further attempts to examine neuroendocrine alterations in depressed epileptics could be undertaken: for example, following up the growing literature on abnormalities of TSH (thyroid stimulating hormone) release in depression after provocative tests (Loosen and Prange 1982).

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APPENDICES

APPENDIX 1: RESEARCH DIAGNOSTIC CRITERIA FOR MAJOR DEPRESSIVE DISORDER

Criteria for Major Depressive Disorder
A. One or more distinct periods with dysphoric mood or pervasive loss of interest or pleasure. The disturbance is characterized by symptoms such as the following: depressed, sad, blue, hopeless, low, down in the dumps, "don't care any more," or irritable. The disturbance must be prominent and relatively persistent but not necessarily the most dominant symptom. It does not include momentary shifts from one dysphoric mood to another dysphoric mood, eg, anxiety to depression to anger, such as are seen in states of acute psychotic turmoil.
B. At lease five of the following symptoms are required to have appeared as part of the episode for definite and four for probable (for past episodes, because of memory difficulty, one less symptom is required). 1. Poor appetite or weight loss or increased appetite or weight gain (change of 0.5 kg a week over several weeks or 4.5 kg a year when dieting) 2. Sleep difficulty or sleeping too much 3. Loss of energy, fatigability, or tiredness 4. Psychomotor agitation or retardation (but not mere subjective feeling of restlessness or being slowed down) 5. Loss of interest or pleasure in usual activities, including social contact or sex (do not include if limited to a period when delusional or hallucinating) (The loss may or may not be pervasive.) 6. Feeling of self-reproach or excessive or inappropriate guilt (either may be delusional) 7. Complaints or evidence of diminished ability to think or concentrate, such as slowed thinking, or indecisiveness (do not include if associated with marked formal thought disorder) 8. Recurrent thoughts of death or suicide, or any suicidal behavior
C. Duration of dysphoric features at least one week, beginning with the first noticeable change in the subject's usual condition (definite if lasted more than two weeks, probable if one to two weeks).
D. Sought or was referred for help from someone during the dysphoric period, took medication, or had impairment in functioning with family, at home, at school, at work, or socially.
E. None of the following that suggest schizophrenia is present: 1. Delusions of being controlled (or influenced), or of thought broadcasting, insertion, or withdrawal (as defined in this manual) 2. Nonaffective hallucinations of any type (as defined in this manual) throughout the day for several days or intermittently throughout a one-week period 3. Auditory hallucinations in which either a voice keeps up a running commentary on the subject's behaviors or thoughts as they occur, or two or more voices converse with each other 4. At some time during the period of illness had more than one month when he exhibited no prominent depressive symptoms but had delusions or hallucinations (although typical depressive delusions such as delusions of guilt, sin, poverty, nihilism, or self-deprecation, or hallucinations with similar content are not included) 5. Preoccupation with a delusion or hallucination to the relative exclusion of other symptoms or concerns (other than typical depressive delusions of guilt, sin, poverty, nihilism, self-deprecation or hallucinations with similar content) 6. Definite instances of marked formal thought disorder (as defined in this manual), accompanied by either blunted or inappropriate affect, delusions or hallucinations of any type, or grossly disorganized behavior
F. Does not meet the criteria for schizophrenia, residual subtype.

APPENDIX 2: A CLASSIFICATION OF HAND PREFERENCE

NAME_____AGE_____ SEX_____

Were you one of twins, triplets at birth or were you single born?

Please indicate which hand you habitually use for each of the following activities by writing R (for right), L (for left), E (for either).

Which hand do you use:

1. To write a letter legibly? .....
2. To throw a ball to hit a target? .....
3. To hold a racket in tennis, squash or badminton? .....
4. To hold a match whilst striking it? .....
5. To cut with scissors? .....
6. To guide a thread through the eye of a needle (or guide needle on to thread)? .....
7. At the top of a broom while sweeping? .....
8. At the top of a shovel when moving sand? .....
9. To deal playing cards? .....
10. To hammer a nail into wood? .....
11. To hold a toothbrush while cleaning your teeth? .....
12. To unscrew the lid of a jar? .....

If you use the RIGHT HAND FOR ALL OF THESE ACTIONS, are there any one-handed actions for which you use the LEFT HAND? Please record them here .....

.....

If you use the LEFT HAND FOR ALL OF THESE ACTIONS, are there any one-handed actions for which you use the RIGHT HAND? Please record them here.....

.....

APPENDIX 3: HAMILTON DEPRESSION RATING SCALE

No.	Symptoms	Points
1	DEPRESSED MOOD (0-4) Gloomy attitude, pessimism about future, feeling of sadness, tendency to weep. 1 = sadness etc. 2 = occasional weeping 3 = frequent weeping 4 = extreme symptoms	
2	GUILT (0-4) 1 = self reproach, feels he has let people down 2 = ideas of guilt 3 = present illness is a punishment, delusions of guilt 4 = hallucinations of guilt	
3	SUICIDE (0-4) 1 = feels life is not worth living 2 = wishes he were dead 3 = suicide ideas 4 = attempts at suicide	
4	INSOMNIA INITIAL (0-2) 1 = occasional difficulty in falling asleep 2 = nightly difficulty in falling asleep	
5	INSOMNIA MIDDLE (0-2) 1 = patient restless and disturbed during the night 2 = waking during the night	
6	INSOMNIA DELAYED (0-2) 1 = waking in early hours, but returning to sleep 2 = unable to fall asleep again	
7	WORK AND INTERESTS (0-4) 1 = thoughts, feelings of incapacity or weakness relating to activities 2 = loss of interest in activity, hobbies or work 3 = decrease in time spent in activities or decrease in productivity 4 = unable to work because of present illness	
8	RETARDATION (0-4) 1 = slight retardation at interview 2 = obvious retardation at interview 3 = interview difficult 4 = complete stupor, mute	
9	AGITATION (0-4) 1 = fidgetiness 2 = playing with hands, hair, etc. 3 = moving about, can't sit still 4 = hand wringing, nail biting, hair pulling, etc.	

APPENDIX 3 CONTINUED

No.	Symptoms	Points
10	ANXIETY PSYCHIC (0-4) 1 = tension and irritability 2 = worrying about minor matters 3 = apprehensive attitude 4 = fears	
11	ANXIETY SOMATIC (0-4) 1 = mild 2 = moderate wind, indigestion, diarrhoea, cramps 3 = severe palpitations, headaches, etc. 4 = incapacitating	
12	SOMATIC SYMPTOMS G I (0-2) 1 = loss of appetite, heavy feeling in abdomen 2 = constipation	
13	SOMATIC SYMPTOMS GENERAL (0-2) 1 = heaviness in limbs, back or head, diffuse backache 2 = definite symptoms rates 2	
14	GENITAL SYMPTOMS (0-2) 1 = mild 2 = severe e.g. loss of libido, menstrual disturbances	
15	HYPOCHONDRIASIS (0-4) 1 = self absorption (bodily) 2 = preoccupation with health 3 = frequent complaints 4 = hypochrondriacal delusion	
16	LOSS OF WEIGHT (0-2) 1 = probably weight loss associated with illness 2 = definite weight loss (according to patient)	
17	INSIGHT (0-2) 1 = acknowledges illness, but attributes cause to food, climate, need for rest, etc. 2 = denies being ill at all	
18	DIURNAL VARIATION (0-2) 1 = worse a.m. 2 = worse p.m.	
19	DEPERSONALISATION AND DEREALISATION (0-4) 1 = mild 2 = moderate e.g. feelings of 3 = severe 4 = incapacitating unreality, nihilistic ideas	
20	PARANOID SYMPTOMS (0-4) 1 = suspicous 2 = ideas of reference 3 = delusions of reference and persecution 4 = hallucinations, persecutory	
21	OBSESSIONAL SYMPTOMS (0-2) 1 = mild 2 = severe obsessive thoughts and compulsions against which patient struggles	

APPENDIX 4: BECK DEPRESSION INVENTORY

☐	I do not feel sad
☐	I feel blue or sad
☐	I am blue or sad all the time and I can't snap out of it.
☐	I am so sad or unhappy that it is very painful.
☐	I am so sad or unhappy that I can't stand it.
☐	I am not particularly pessimistic or discouraged about the future.
☐	I feel discouraged about the future.
☐	I feel I have nothing to look forward to.
☐	I feel I won't ever get over my troubles.
☐	I feel that the future is hopeless and that things cannot improve.
☐	I do not feel like a failure
☐	I feel I have failed more than the average person.
☐	I feel I have accomplished very little that is worthwhile or that means anything.
☐	As I look back of my life all I can see is a lot of failure.
☐	I feel I am a complete failure as a person (parent, husband, wife).
☐	I am not particularly dissatisfied.
☐	I feel bored most of the time.
☐	I don't enjoy things the way I used to.
☐	I don't get satisfaction out of anything any more.
☐	I am dissatisfied with everything.
☐	I don't feel particularly guilty.
☐	I feel bad or unworthy a good part of the time.
☐	I feel quite guilty.
☐	I feel bad or unworthy practically all the time now.
☐	I feel as though I am very bad or worthless.
☐	I don't feel I am being punished.
☐	I have a feeling that something bad may happen to me.
☐	I feel I am being punished or will be punished.
☐	I feel I deserve to be punished.
☐	I want to be punished.
☐	I don't feel disappointed in myself.
☐	I am disappointed in myself.
☐	I don't like myself.
☐	I am disgusted with myself.
☐	I hate myself.

APPENDIX 4 CONTINUED

- ☐ I don't feel I am any worse than anybody else.
- ☐ I am critical of myself for my weaknesses or mistakes.
- ☐ I blame myself for my faults.
- ☐ I blame myself for everything bad that happens.

- ☐ I don't have any thoughts of harming myself.
- ☐ I have thoughts of harming myself but I would not carry them out.
- ☐ I feel I would be better off dead.
- ☐ I feel my family would be better off if I were dead.
- ☐ I have definite plans about committing suicide.
- ☐ I would kill myself if I could.

- ☐ I don't cry any more than usual.
- ☐ I cry more now than I used to.
- ☐ I cry all the time now - I can't stop it.
- ☐ I used to be able to cry but now I can't cry at all even though I want to.

- ☐ I am no more irritated now than I ever am.
- ☐ I get annoyed or irritated more easily than I used to.
- ☐ I feel irritated all the time.
- ☐ I don't get irritated at all at the things that used to irritate me.

- ☐ I have not lost interest in other people.
- ☐ I am less interested in other people now than I used to be.
- ☐ I have lost most of my interest in other people and have little feeling for them.
- ☐ I have lost all my interest in other people and don't care about them at all.

- ☐ I make decisions about as well as ever.
- ☐ I try to put off making decisions.
- ☐ I have great difficulty in making decisions.
- ☐ I can't make any decisions at all any more.

- ☐ I don't feel I look any worse than I used to.
- ☐ I am worried that I am looking old and unattractive.
- ☐ I feel that there are permanent changes in my appearance and they make me look unattractive.
- ☐ I feel that I am ugly or repulsive-looking.

- ☐ I can work about as well as before.
- ☐ It takes extra effort to get started at doing something.
- ☐ I don't work as well as I used to.
- ☐ I have to push myself very hard to do anything.
- ☐ I can't do any work at all.

APPENDIX 4 CONTINUED

- ☐ I can sleep as well as usual.
- ☐ I wake up more tired in the morning than I used to.
- ☐ I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
- ☐ I wake up early every day and can't get more than 5 hours' sleep.

- ☐ I don't get any more tired than usual
- ☐ I get tired more easily than I used to be.
- ☐ I get tired from doing anything.
- ☐ I get too tired to do anything.

- ☐ My appetite is no worse than usual.
- ☐ My appetite is not as good as it used to be.
- ☐ My appetite is much worse now.
- ☐ I have no appetite at all any more.

- ☐ I haven't lost much weight, if any, lately.
- ☐ I have lost more than 5 pounds.
- ☐ I have lost more than 10 pounds.
- ☐ I have lost more than 15 pounds.

- ☐ I am no more concerned about my health than usual.
- ☐ I am concerned about aches and pains, or upset stomach, or constipation.
- ☐ I am so concerned with how I feel or what I feel that it's hard to think of much else.
- ☐ I am completely absorbed in what I feel.

- ☐ I have not noticed any recent change in my interest in sex.
- ☐ I am less interested in sex than I used to be.
- ☐ I am much less interested in sex now.
- ☐ I have lost interest in sex completely.

APPENDIX 5

L.P.D. QUESTIONNAIRE

NAME (in full) ..... DATE .....
(MR.,MRS.,MISS)
.....

AGE ..... RELIGION ..... OCCUPATION .....

MARRIED. SINGLE. WIDOWED. DIVORCED OR SEPARATED. .....
(Please tick where appropriate.)

How long have you been ill? .....

INSTRUCTIONS: Please answer these questions as quickly as possible.

Put a circle round your answer.

1. Are you more irritable towards other people? .. .. Yes No
2. Have you lost interest in watching television? .. .. Yes No
3. Do you have difficulty in falling asleep without tablets? .. Yes No
4. Do you feel depressed all day long? .. .. Yes No
5. Do you feel slowed up in your thinking? .. .. Yes No
6. Have you any serious money worries? .. .. Yes No
7. Have you had any recent family worries? .. .. Yes No
8. Have you lost someone you love in the past year? .. .. Yes No
9. Do you feel you are a bad person?.. .. .. Yes No
10. Have you moved house in the past year? .. .. Yes No
11. Do you avoid company?.. .. .. Yes No
12. Is it more difficult to concentrate on your work? .. .. .. Yes No
13. Have you any housing worries? .. .. Yes No
14. Do you wish you were able to cry? .. .. Yes No
15. Do you have a restless and disturbed sleep without tablets? .. Yes No
16. Do you feel most depressed in the evenings? .. .. Yes No
17. Are there time when you do not feel depressed? .. .. Yes No
18. Do you have less interest in reading newspapers? .. .. Yes No
19. Do you think you will get better? .. .. Yes No
20. Do you feel that people are sometimes talking about you? .. .. Yes No
21. Is it easy to fall asleep without tablets? .. .. Yes No
22. Is your appetite normal? .. .. Yes No
23. Have you less interest in sex? .. .. Yes No
24. Do you feel you are a burden to others? .. .. Yes No

APPENDIX 5 CONTINUED

25. Is life worth living? .. .. Yes No

26. Do you cry a lot? .. .. Yes No

27. Are you unable to cry? . .. . Yes No

28. Have you become constipated? .. .. Yes No

29. Do you feel happier in the mornings? .. .. Yes No

30. Do you suffer from a dry mouth? .. .. Yes No

31. Have you less feeling for those close to you? .. .. Yes No

32. Do you feel you are letting other people down? . .. . Yes No

33. Have you lost your appetite? .. .. Yes No

34. Have you had trouble at work in the past year? . .. . Yes No

35. Do you wish you were dead? . .. . Yes No

36. Do you waken much earlier than your usual time without tablets? .. Yes No

37. Are you as good a person as most of your friends? . .. . Yes No

38. Do you feel less depressed when you are with company? .. .. Yes No

39. Do you think that your illness is a punishment that you deserve? .. Yes No

40. Do you have less interest in things you usually enjoy? . .. . Yes No

41. Can you sleep normally without tablets? .. .. Yes No

42. Do you waken at your usual time without tablets? .. .. Yes No

43. Do you think there is something seriously wrong with your body? .. Yes No

44. Is your depression the same all day long? .. .. Yes No

45. Do you find difficulty in relaxing?. .. .. Yes No

46. Do you feel life is not worth living? .. .. Yes No

47. Have you lost weight? .. .. Yes No

48. Do you feel most depressed in the mornings? .. .. Yes No

49. Have you overheard people talking about you? .. .. Yes No

50. Do you feel this illness has been brought upon you by yourself? .. Yes No

51. Do you feel slowed up doing things? .. .. Yes No

52. Does the future look hopeful? .. .. Yes No

53. Do you feel happier in the evenings? ... . Yes No

54. Have you thought recently about ending your life? .. .. Yes No

55. Do you feel time passing more slowly? .. .. Yes No

56. Are you doing your work as well as you used to? .. .. Yes No

57. Can you be easily cheered up? .. .. Yes No

APPENDIX 6: THE NEWCASTLE DIAGNOSTIC SCALE - WEIGHTINGS AND DEFINITIONS

Item	Weighted Score	Defined	Definition
1. Adequate personality	+1	Newcastle 1965	This describes subjects free from any history of neurotic breakdown and without disabling neurotic symptoms or serious social maladjustment.
2. No adequate psychogenesis	+2	Newcastle 1965	No psychological stress or difficulty continuing to operate after the onset of symptoms and adequate to explain perpetuation of the illness.
3. Distinct quality	+1	Newcastle 1965	Some patients may describe their depression as similar to "normal" sadness or gloom differing in degree only: others give a description of depression having a quality distinct from the mood with which the patient usually reacts to adversity. (Patients may even deny depression despite ample objective evidence to the contrary and instead refer to an "indescribable mood state"). It is to the latter type of depression that this feature refers.
4. Weight loss greater than 7 lbs.	+2		Weight loss associated with present illness.
5. Previous episode	+1		Of depressive illness.
6. Depressive psychomotor activity	+2	Newcastle 1965	This term is used to describe any objective evidence of psychomotor slowing, stupor or agitation.
7. Anxiety	-1	Schalling et al 1973	Unpleasant emotional state characterised by an unpleasant feeling tone which is related to that of fear, but has less specific or less relevant cues.
8. Nihilistic delusions	+2	Newcastle (1965)	Delusions of doom, imminent destruction, somatic dissolution or poverty of the patient and his family.
9. Blames others	-1		Blames other people for his present condition.
10. Guilt	+1	No definition but note (1965) that:	Feelings of guilt are weighted equal to delusions of guilt.

APPENDIX 7a: STAI STATE QUESTIONNAIRE

S-B. QUESTIONNAIRE

NAME _____ DATE _____

DIRECTIONS. Read each statement and then tick to indicate how you feel right now, that is, at this moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	NOT AT ALL	SOME-WHAT	MODERATELY SO	VERY MUCH SO
1. I feel calm	☐	☐	☐	☐
2. I feel secure	☐	☐	☐	☐
3. I am tense	☐	☐	☐	☐
4. I am regretful	☐	☐	☐	☐
5. I feel at ease	☐	☐	☐	☐
6. I feel upset	☐	☐	☐	☐
7. I am presently worrying over possible misfortunes	☐	☐	☐	☐
8. I feel rested	☐	☐	☐	☐
9. I feel anxious	☐	☐	☐	☐
10. I feel comfortable	☐	☐	☐	☐
11. I feel self-confident	☐	☐	☐	☐
12. I feel nervous	☐	☐	☐	☐
13. I am jittery	☐	☐	☐	☐
14. I feel "high strung"	☐	☐	☐	☐
15. I am relaxed	☐	☐	☐	☐
16. I feel content	☐	☐	☐	☐
17. I am worried	☐	☐	☐	☐
18. I feel over-excited and "rattled"	☐	☐	☐	☐
19. I feel joyful	☐	☐	☐	☐
20. I feel pleasant	☐	☐	☐	☐

APPENDIX 7b: STAI TRAIT QUESTIONNAIRE

NAME _____ DATE _____

DIRECTIONS. Read each statement and then tick to indicate how you generally feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

	ALMOST NEVER	SOME-TIMES	OFTEN	ALMOST ALWAYS
21. I feel pleasant	☐	☐	☐	☐
22. I tire quickly	☐	☐	☐	☐
23. I feel like crying	☐	☐	☐	☐
24. I wish I could be as happy as others seem to be	☐	☐	☐	☐
25. I am losing out on things because I can't make up my mind soon enough	☐	☐	☐	☐
26. I feel rested	☐	☐	☐	☐
27. I am "calm, cool, and collected"	☐	☐	☐	☐
28. I feel that difficulties are piling up so that I cannot overcome them	☐	☐	☐	☐
29. I worry too much over something that really doesn't matter	☐	☐	☐	☐
30. I am happy	☐	☐	☐	☐
31. I am inclined to take things hard	☐	☐	☐	☐
32. I lack self-confidence	☐	☐	☐	☐
33. I feel secure	☐	☐	☐	☐
34. I try to avoid facing a crisis or difficulty	☐	☐	☐	☐
35. I feel blue	☐	☐	☐	☐
36. I am content	☐	☐	☐	☐
37. Some unimportant thought runs through my mind and bothers me	☐	☐	☐	☐
38. I take disappointments so keenly that I can't put them out of my mind	☐	☐	☐	☐
39. I am a steady person	☐	☐	☐	☐
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	☐	☐	☐	☐

APPENDIX 8: HOSTILITY AND DIRECTION OF HOSTILITY QUESTIONNAIRE

1. Most people make friends because friends are likely to be useful to them .	True	False
2. I do not blame a person for taking advantage of someone who lays himself open to it	True	False
3. I usually expect to succeed in things I do	True	False
4. I have no enemies who really wish to harm me	True	False
5. I wish I could get over worrying about things I have said that may have injured other people's feelings	True	False
6. I think nearly anyone would tell a lie to keep out of trouble . . .	True	False
7. I don't blame anyone for trying to grab everything he can get in this world	True	False
8. My hardest battles are with myself	True	False
9. I know who, apart from myself, is responsible for most of my troubles .	True	False
10. Some people are so bossy that I feel like doing the opposite of what they request, even though I know they are right	True	False
11. Some of my family have habits that bother and annoy me very much . .	True	False
12. I believe my sins are unpardonable	True	False
13. I have very few quarrels with members of my family	True	False
14. I have often lost out on things because I couldn't make up my mind soon enough	True	False
15. I can easily make other people afraid of me, and sometimes do for the fun of it	True	False
16. I believe I am a condemned person	True	False
17. In school I was sometimes sent to the principal for misbehaving . .	True	False
18. I have at times stood in the way of people who were trying to do something, not because it amounted to much but because of the principle of the thing	True	False
19. Most people are honest chiefly through fear of being caught . . .	True	False
20. Sometimes I enjoy hurting persons I love	True	False
21. I have not lived the right kind of life	True	False
22. Sometimes I feel as if I must injure either myself or someone else . .	True	False
23. I seem to be about as capable and clever as most others around me . .	True	False
24. I sometimes tease animals	True	False

APPENDIX 8 CONTINUED

25. I get angry sometimes . . . . . True False

26. I am entirely self-confident . . . . . True False

27. Often I can't understand why I have been so cross and grouchy . . . True False

28. I shrink from facing a crisis or difficulty . . . . . True False

29. I think most people would lie to get ahead . . . . . True False

30. I have sometimes felt that difficulties were piling up so high that I could not overcome them . . . . . True False

31. If people had not had it in for me I would have been much more successful True False

32. I have often found people jealous of my good ideas, just because they had not thought of them first . . . . . True False

33. Much of the time I feel as if I have done something wrong or evil . . True False

34. I have several times given up doing a thing because I thought too little of my ability . . . . . True False

35. Someone has it in for me . . . . . True False

36. When someone does me a wrong I feel I should pay him back if I can, just for the principle of the thing . . . . . True False

37. I am sure I get a raw deal from life. . . . . True False

38. I believe I am being followed . . . . . True False

39. At times I have a strong urge to do something harmful or shocking . . True False

40. I am easily downed in an argument. . . . . True False

41. It is safer to trust nobody . . . . . True False

42. I easily become impatient with people . . . . . True False

43. At times I think I am no good at all . . . . . True False

44. I commonly wonder what hidden reason another person may have for doing something nice for me . . . . . True False

45. I get angry easily and then get over it soon . . . . . True False

46. At times I feel like smashing things. . . . . True False

47. I believe I am being plotted against. . . . . True False

48. I certainly feel useless at times . . . . . True False

49. At times I feel like picking a fist fight with someone . . . . . True False

50. Someone has been trying to rob me . . . . . True False

51. I am certainly lacking in self-confidence . . . . . True False

Please check to see that you have given answers for every statement.

E ○ N ○ L ○

FORM A

		YES	NO
1.	Do you often long for excitement?	○	○
2.	Do you often need understanding friends to cheer you up?	○	○
3.	Are you usually carefree?	○	○
4.	Do you find it very hard to take no for an answer?	○	○
5.	Do you stop and think things over before doing anything?	○	○
6.	If you say you will do something do you always keep your promise, no matter how inconvenient it might be to do so?	○	○
7.	Does your mood often go up and down?	○	○
8.	Do you generally do and say things quickly without stopping to think?	○	○
9.	Do you ever feel "just miserable" for no good reason?	○	○
10.	Would you do almost anything for a dare?	○	○
11.	Do you suddenly feel shy when you want to talk to an attractive stranger?	○	○
12.	Once in a while do you lose your temper and get angry?	○	○
13.	Do you often do things on the spur of the moment?	○	○
14.	Do you often worry about things you should not have done or said?	○	○
15.	Generally, do you prefer reading to meeting people?	○	○
16.	Are your feelings rather easily hurt?	○	○
17.	Do you like going out a lot?	○	○
18.	Do you occasionally have thoughts and ideas that you would not like other people to know about?	○	○
19.	Are you sometimes bubbling over with energy and sometimes very sluggish?	○	○
20.	Do you prefer to have few but special friends?	○	○
21.	Do you daydream a lot?	○	○
22.	When people shout at you, do you shout back?	○	○
23.	Are you often troubled about feelings of guilt?	○	○
24.	Are *all* your habits good and desirable ones?	○	○
25.	Can you usually let yourself go and enjoy yourself a lot at a lively party?	○	○
26.	Would you call yourself tense or "highly-strung"?	○	○
27.	Do other people think of you as being very lively?	○	○
28.	After you have done something important, do you often come away feeling you could have done better?	○	○
29.	Are you mostly quiet when you are with other people?	○	○
30.	Do you sometimes gossip?	○	○
31.	Do ideas run through your head so that you cannot sleep?	○	○
32.	If there is something you want to know about, would you rather look it up in a book than talk to someone about it?	○	○
33.	Do you get palpitations or thumping in your heart?	○	○
34.	Do you like the kind of work that you need to pay close attention to?	○	○
35.	Do you get attacks of shaking or trembling?	○	○
36.	Would you always declare *everything* at the customs, even if you knew that you could never be found out?	○	○
37.	Do you hate being with a crowd who play jokes on one another?	○	○
38.	Are you an irritable person?	○	○
39.	Do you like doing things in which you have to act quickly?	○	○
40.	Do you worry about awful things that might happen?	○	○
41.	Are you slow and unhurried in the way you move?	○	○
42.	Have you ever been late for an appointment or work?	○	○
43.	Do you have many nightmares?	○	○
44.	Do you like talking to people so much that you never miss a chance of talking to a stranger?	○	○
45.	Are you troubled by aches and pains?	○	○
46.	Would you be very unhappy if you could not see lots of people most of the time?	○	○
47.	Would you call yourself a nervous person?	○	○
48.	Of all the people you know, are there some whom you definitely do not like?	○	○
49.	Would you say that you were fairly self-confident?	○	○
50.	Are you easily hurt when people find fault with you or your work?	○	○
51.	Do you find it hard to really enjoy yourself at a lively party?	○	○
52.	Are you troubled with feelings of inferiority?	○	○
53.	Can you easily get some life into a rather dull party?	○	○
54.	Do you sometimes talk about things you know nothing about?	○	○
55.	Do you worry about your health?	○	○
56.	Do you like playing pranks on others?	○	○
57.	Do you suffer from sleeplessness?	○	○

PLEASE CHECK TO SEE THAT YOU HAVE ANSWERED *ALL* THE QUESTIONS

APPENDIX 10

P. AND P. I. QUESTIONNAIRES

SELF-DESCRIPTION QUESTIONNAIRE (HOQ)

by T. M. CAINE

SURNAME_____ CHRISTIAN NAMES_____

AGE____ SEX_____ OCCUPATION_____ MARITAL STATUS_____ DATE_____

Instructions :—

Read over each question and decide whether it is a true description of how you usually act or feel, then put a circle round "True" if the statement describes you or round "False" if it does not. Do not spend too much time over any question. Take your first reaction bearing in mind your usual way of acting or feeling. Do not miss any question. There are no right or wrong answers.

1. I find it hard to think up stories	True	False
2. I like to wear eye-catching clothes	True	False
3. I keep my feelings to myself	True	False
4. I am slow in making up my mind about things because I weigh up all the pros and cons	True	False
5. I am a moody sort of person, with lasting moods	True	False
6. I have rigid standards I feel I should stick to	True	False
7. When I am working I like a job which calls for speed rather than close attention to details	True	False
8. I like to ask for other people's opinions and advice about myself	True	False
9. I don't feel awkward when meeting people because I know how to behave	True	False
10. I prefer to be popular with everyone than to have a few deep lasting friendships	True	False
11. I cannot shake off my troubles easily even if I get the opportunity	True	False
12. I have a good imagination	True	False
13. I keep quiet at parties or meetings	True	False
14. I feel better after I've had a good row and got it off my chest	True	False
15. I am quick in sizing up people and situations	True	False
16. My mood is easily changed by what happens around me	True	False
17. My conscience seldom bothers me	True	False
18. I keep a place for everything and everything in its place	True	False
19. I'm rather lacking in the social graces	True	False
20. I have the same friends now as I had years ago	True	False
21. It pleases me to be the centre of a lively group	True	False
22. I like to show people exactly how I feel about things	True	False
23. The first impressions or reactions are usually the right ones in the end	True	False
24. I do not mind if things turn out badly as long as I know I've done the right thing	True	False

APPENDIX 10 CONTINUED

25. I can lead more than one life in my imagination	True	False
26. I like discussing myself with other people	True	False
27. I do not show my emotions in front of people	True	False
28. When someone asks me a question I give a quick answer and look for the reasons later	True	False
29. If I am not in the right mood for something it takes a lot to make me feel differently	True	False
30. I usually get by without having to worry about whether I've done the right thing morally or not	True	False
31. One can understand most things without having to go into all the details .	True	False
32. It is important to be fashionable in your opinions, clothes, etc.	True	False
33. My party manners are pretty good	True	False
34. The only friends I make I keep	True	False
35. If I happen to be upset about something it seems to carry over into all I do for a long time	True	False
36. I cannot completely lose myself in a book or story	True	False
37. I like to sit in the background or in an inconspicuous place at socials, meetings, etc.	True	False
38. I act out my feelings	True	False
39. I wait until I am sure of all my facts before I make a decision	True	False
40. I spend a good deal of time worrying about the rights and wrongs of conduct	True	False
41. When going into a room or meeting someone for the first time I get a strong general impression first and only gradually take in the details . . .	True	False
42. When meeting people I haven't met before I usually feel I make a rather poor impression	True	False
43. It upsets me to leave friends and make new ones even if I have to. . .	True	False
44. When watching a play I identify myself with the characters	True	False
45. My feelings about things and towards other people seldom change . .	True	False
46. I do not like taking a leading part in group activities	True	False
47. Mistakes are usually made when people make snap decisions	True	False
48. If two people find they disagree about things they shouldn't try to carry on being close friends	True	False

APPENDIX 11: SIDE EFFECTS SCALE

Dryness of the mouth
Disturbances of accommodation
Disturbances of urination
Constipation
Palpitations/tachycardia
Dizziness
Syncope/tendency to syncope
Headache
Increased sweating
Insomnia
Drowsiness
Akinesia
Parkinsonism
Acute dystonia
Akathisia
Tardive dyskinesia
Pruritus/rash
Dyspepsia/nausea/vomiting
Other

APPENDIX 12: CLINICAL DETAILS OF PATIENTS WHO COMPLETED THE DOUBLE BLIND ANTIDEPRESSANT TRIAL

	Patients on Amitriptyline	Patients on Nomifensine	Patients on Placebo
Sex:			
Male	4	5	4
Female	9	8	9
Age in Years:			
Range	23 - 59	18 - 60	19 - 52
Mean	39.6	33.5	35.5
SD	9.9	13.2	10.7
Age of Onset of Epilepsy:			
Range	6 - 56	6 - 57	4 - 46
Mean	21.3	18.8	19.1
SD	14.1	14.1	10.1
Duration of Epilepsy:			
Range	3 - 39	3 - 32	1 - 42
Mean	18.3	14.8	16.5
SD	9.6	10.2	11.0
Seizure Type:			
Primary Generalised	2	5	0
Secondarily Generalised	2	1	5
Partial Complex	6	3	3
Partial Complex Secondarily Generalised	2	3	5
Partial Simple	1	0	0
Unclassifiable	0	1	0
EEG Abnormality:			
Normal	2	2	1
Generalised Diffuse	2	5	5
Left Temporal	3	2	5
Right Temporal	1	2	1
Bilateral Temporal	1	1	0
Non-specific	3	0	1
Other	1	1	0
Newcastle Classification:			
Endogenous	1	7	4
Non-endogenous	12	6	9
LPD Classification:			
Endogenous	6	4	3
Non-endogenous	4	5	8
Non-depressed	3	4	2
Psychotic:			
Yes	2	3	2
No	11	10	11
HDRS (21 item):			
Range	15 - 33	16 - 31	16 - 33
Mean	21.4	24.3	23.1
SD	5.0	5.3	5.5

APPENDIX 12 CONTINUED

	Patients on Amitriptyline	Patients on Nomifensine	Patients on Placebo
BDI Score:			
Range	12 - 35	6 - 32	9 - 39
Mean	24.2	22.7	25.2
SD	10.0	7.1	8.4
LPD D Score:			
Range	9 - 17	6 - 15	5 - 18
Mean	12.7	11.7	12.8
SD	3.0	2.7	3.8
STAI-State Score:			
Range	30 - 68	32 - 78	45 - 78
Mean	55.7	57.6	60.4
SD	11.1	14.5	10.1
STAI-Trait Score:			
Range	33 - 72	45 - 77	32 - 70
Mean	57.9	59.8	56.3
SD	11.9	9.3	11.3
Suicidal Behaviour:			
Yes	8	7	2
No	5	6	11
Seizure Frequency Prior to Onset of Depression:			
Increased	0	1	2
Decreased	6	6	3
Same	7	6	8
Number of Seizures in Past 2 Weeks:			
0	7	6	5
1 - 5	3	4	3
6 - 10	1	1	1
11 - 20	0	0	0
Over 20	0	0	1
Unknown	2	2	3

APPENDIX 13: MEANS AND STANDARD DEVIATIONS OF THE SCORES OF THE RATING SCALES OVER THE 6 WEEK DOUBLE BLIND TRIAL

	Week 0		Week 2		Week 4		Week 6	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
21 item HDRS								
Amitriptyline	21.4	5.0	16.2	5.3	13.9	6.7	14.1	7.4
Nomifensine	24.3	5.3	15.1	6.6	11.2	5.1	12.2	6.6
Placebo	23.6	6.3	14.0	6.5	14.6	8.4	12.9	7.0
BDI								
Amitriptyline	25.0	9.7	19.3	9.7	18.1	10.5	16.5	9.6
Nomifensine	22.7	7.1	18.3	9.1	14.6	8.8	14.2	11.0
Placebo	26.3	8.6	17.2	10.1	17.8	10.8	15.5	10.5
STAI A-State								
Amitriptyline	57.5	6.9	54.7	9.3	51.2	9.5	51.8	14.1
Nomifensine	57.6	14.5	51.4	10.2	49.6	14.3	49.3	12.7
Placebo	60.4	10.1	50.7	17.8	54.4	12.1	48.5	12.5

APPENDIX 14: SERUM ANTICONVULSANT LEVELS OF PATIENTS ON ANTICONVULSANT MONOTHERPAY

Patient Number	Anticonvulsant	Antidepressant Placebo	Week Number	Serum Anticonvulsant Level (μmol/L)				Comments
				09.00 hrs	Mean	13.00 hrs	Mean	
13	DPH	Nomifensine	0	43	-	-	-	
			2	40		42		
			4	36	38	35	40	
			6	39		44		Inconsistent DPH changes
			8	40		30		
			10	47	42	44	39	
			12	40		43		
17	DPH	Nomifensine	0	41	-	-	-	
			2	40		36		
			4	28	34	37	35	
			6	33		33		Inconsistent DPH changes
			8	34		30		
			10	36	37	37	34	
			12	41		34		
31 (Admitted non-compliance)	DPH	Nomifensine	0	42	-	-	-	
			2	58		60		
			4	59	51	54	50	(Excluded)
			6	37		36		
			8	13		9		
			10	14	26	12	22	
			12	50		46		
35	DPH	Nomifensine	0	59	-	-	-	
			2	52		51		
			4	78	68	74	61	
			6	70		58)		

APPENDIX 14 CONTINUED

Patient Number	Anticonvulsant	Antidepressant Placebo	Week Number	Serum Anticonvulsant Level (μmol/L) 09.00 hrs	Mean	13.00 hrs	Mean	Comments
1	DPH	Amitriptyline	0	25	-	-	-	
			2	28		26		
			4	28	29	25	27	
			6	32		31		
			8	45		43		Overall slight
			10	26	28	20	32	increase of
			12	14		34		DPH
10 (Admitted non-compliance)	DPH	Amitriptyline	0	38	-	-	-	
			2	30		27		
			4	31	29	28	29	
			6	27		33		(Excluded)
			8	37		41		
			10	29	34	30	35	
			12	36		34		
18	DPH	Amitriptyline	0	34	-	-	-	
			2	49		45		
			4	35	43	32	39	
			6	46		40		
			8	46		39		
			10	48	43	45	38	
			12	36		31		
39	DPH	Placebo	0	31	-	-	-	
			2	73		34		Increase at 9am
			4	32	51	41	37	Decrease at 1pm
			6	47		35		

APPENDIX 14 CONTINUED

Patient Number	Anticonvulsant	Antidepressant Placebo	Week Number	Serum Anticonvulsant Level (μmol/L) 09.00 hrs	Mean	13.00 hrs	Mean	Comments
40	CBZ	Nomifensine	0	34	-	-	-	
			2	44		53		Slight increase
			4	46	42	36	42	of CBZ
			6	37		36		
36	CBZ	Amitritpyline	0	47	-	-	-	
			2	40		50		
			4	65	47	51	49	
			6	36		45		
37	CBZ	Amitriptyline	0	39	-	-	-	
			2	52		46		
			4	55	52	44	43	
			6	50		39		
			8	35		31		Inconsistent
			10	46	42	41	37	results
			12	45		38		
16	CBZ	Placebo	0	66	-	-	-	
			2	65		53		
			4	52	57	38	45	Inconsistent
			6	55		44		results
30	CBZ	Placebo	0	27	-	-	-	
			2	46		40)		
			4	46	44	35	36	
			6	40		34		

APPENDIX 14 CONTINUED

Patient Number	Anticonvulsant	Antidepressant Placebo	Week Number	Serum Anticonvulsant Level (μmol/L)				Comments
				09.00 hrs	Mean	13.00 hrs	Mean	
8	VPA	Nomifensine	0	467	-	-	-	
			2	935		588		Marked increase
			4	855	912	748	658	of VPA
			6	947		639		
			8	480		391		
			10	613	566	753	688	
			12	606		919		
20	VPA	Nomifensine	0	130	-	-	-	Increase of VPA
			2	208		124		at 9am,
			4	174	187	96	117	decrease at 1pm
			6	179		131		

APPENDIX 15: NUMBER OF PATIENTS REPORTING SIDE EFFECTS

Side Effect	Placebo		Amitriptyline		Nomifensine	
	Week 0	Week 6	Week 0	Week 6	Week 0	Week 6
Dry mouth	7	4	4	8	6	5
Difficulty with accommodation	5	1	4	6	4	2
Urinary disturbance	0	0	2	1	2	2
Constipation	6	4	4	6	4	2
Palpitations	6	2	6	4	7	5
Dizziness	6	5	6	7	6	3
Syncope	0	1	0	1	0	0
Headache	11	10	4	5	10	6
Sweating	7	5	7	5	6	5
Insomnia	8	5	9	4	6	4
Drowsiness	9	7	9	8	8	5
Extrapyramidal reactions	0	0	0	0	0	0
Rash	1	1	0	0	0	0
Gastrointestinal symptoms	2	2	2	0	2	0
Other side effects	0	0	0	0	0	0

APPENDIX 16: SERUM AMITRIPTYLINE LEVELS OF PATIENTS IN THE 12 WEEK STUDY

Patient	Week Number	Serum Amitriptyline Levels (ng/ml)			
		09.00 hrs	Mean	13.00 hrs	Mean
1	2	73		46	
	4	84	87	53	54
	6	103		62	
	8	147		112	
	10	158	153	118	115
	12	-		-	
10	2	43		39	
	4	40	53	17	34
	6	77		46	
	8	154		151	
	10	-	154	-	134
	12	154		116	
15	2	28		18	
	4	-	30	-	19
	6	32		20	
	8	57		39	
	10	71	60	-	35
	12	52		31	
18	2	51		24	
	4	35	46	27	27
	6	53		30	
	8	114		58	
	10	-	114	-	58
	12	-		-	
37	2	86		64	
	4	77	77	58	61
	6	68		61	
	8	177		134	
	10	168	160	124	120
	12	136		103	
42	2	95		75	
	4	97	95	65	69
	6	92		68	
	8	205		165	
	10	203	188	129	147
	12	156		148	

APPENDIX 17: SERUM NOMIFENSINE LEVELS OF PATIENTS IN THE 12 WEEK STUDY

Patient	Week Number	Serum Nomifensine Levels (ng/ml)			
		09.00 hrs	Mean	13.00 hrs	Mean
8	2	310	329	47	53
Patient admitted	4	277		43	
non-compliance	6	399		68	
	8	37		00	
	10	-		-	
	12	-		00	
13	2	280	280	484	484
	4	-		-	
	6	-		-	
	8	882	706	142	124
	10	557		90	
	12	680		141	
17	2	364	467	165	89
	4	565		68	
	6	472		35	
	8	-	602	-	165
	10	602		165	
	12	-		-	
31	2	802	377	515	218
	4	276		92	
	6	53		48	
	8	555	752	68	98
	10	871		114	
	12	830		111	
38	2	576	326	76	69
	4	75		66	
	6	-		65	
	8	-	1039	-	1488
	10	-		1834	
	12	1039		1142	