AN INVESTIGATION INTO DOPAMINE FUNCTION IN BIPOLAR AND UNIPOLAR PRIMARY AFFECTIVE DISORDERS MEASURING PROLACTIN WHEN CHALLENGED BY CHLORPROMAZINE AND L-DIHYDROXYPHENYLALANINE

by

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PREFACE

This thesis, from its conception to its practical implementation and its final compilation, is the work of the author, except as indicated in the acknowledgements. It has not been submitted in part or whole to any other university.

The research was conducted at Tara The H. Moross Centre and the Johannesburg Hospital. Professor W. Wessels was the primary supervisor of the project. The late Professor M. Feldman, Professor J. Levine and Professor J. van Rooyen acted as advisers to the author during the course of the research work.

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ABSTRACT

This work is the result of an investigation into aspects of prolactin and dopamine in primary affective disorders. It is introduced by a discussion on the need for obtaining good scientific data on the organic and psychosocial aspects of psychiatric illness, and in particular, primary affective disorders. A short perspective of the history of depressive illness preceeds the review of relevant scientific literature on primary affective disorder. The literature survey covers aspects which indicate organic causal factors as well as viewing numerous organic studies which are thought to be relevant to this investigation. The role of dopamine in motor behaviour is considered in some detail. Psychopharmacological evidence that the mesolimbic and nigrostriatal dopaminergic systems are involved in motor regulation is reviewed. The role of dopamine receptors in motor behaviour is important to the conceptual framework of this thesis. Dopamine D_2 and D_1 receptors are considered and the opposing roles of these receptors is thought to be significant. Drugs affecting manic and depressive phases of primary affective disorders are reviewed. Emphasis is placed on dopaminergic aspects of various drugs in primary affective disorders as with pimozide as an antimanic agent, and nomifensine as an antidepressant. The possible role of noradrenaline in learning and mood regulation and in the dialogue with dopamine is looked at from an experimental and clinical point of view.

Dopaminergic control of prolactin is reviewed and in particular the nature of the D_4 receptor. The fact that these receptors which are on the pituitary mammotrophs have similarities to the D_2 receptors is relevant. Thus considerable commonality exists between the dopaminergic regulation of motor behaviour and regulation of prolactin. Prolactin is used as an index of dopamine function in patients with primary affective disorders. Motor behaviour is strongly influenced by affective disorders.

The central theme of the study itself was to indirectly evaluate dopamine function in primary affective disorder by measuring prolactin levels. As strong tonic inhibition is exerted by dopamine on prolactin, a series of challenges to the dopamine system was decided upon in order to generate a number of serum prolactin values. A dopamine agonist L-dihydroxyphenylalanine (indirect) and an antagonist, chlorpromazine, were used to stress the system mildly.

The procedure was carried out under standard conditions both in the illness phase and upon significant recovery. Both these investigations were conducted in a drug-free state.

The data generated was subjected to statistical analysis. The results of the analysis suggests that prolactin levels are low in depressed patients, and increase upon recovery, while manic patients have elevated levels which decrease with recovery.

The pattern of the curves obtained from the challenge procedure suggests a possible supersensitivity of dopamine receptors in the manic patients. Blunting of responses of depressed patients remains a possibility but a study against normal controls is required to further assess this aspect.

Evidence is therefore found for altered prolactin levels in illness phases of primary affective disorders. This is thought to be due to an abnormality in the dopamine regulation of prolactin.

A discussion on the possible mechanisms and significance of these changes involves Beta-endorphin in an attempt to tie motor changes to mood regulation.

Shortcomings of the study and future implications and developments are considered.

CONTENTS

TABLES

FIGURES

CHAPTER I

INTRODUCTION

Comprehensive understanding of both normal and disturbed behaviour requires that we have a good knowledge of the neurobiophysiology, the psychology and the social and enviromental influences on behaviour. It is only in recent times that good progress is being made in the understanding of the organic aspects of behaviour. The developmentof new techniques of measurement and data collection has made this possible. Psychiatrists who wish to work in this field need to extend their training in the neurosciences. Better insight into the physiology of behaviour should be complementary to the psychosocial aspects of human function, rather than oppositional. This study is in pursuit of a greater understanding of the organic aspects of abnormal behaviour, particularly in a situation where there is evidence for a strong pathophysiological contribution.

The understanding of what appear to be pathological states have a real possibility of improving our concepts of normal physiology. The caricature which certain conditions produce may heighten the probability of seeing the physiological components and thereby not not only contributing to the understanding of the pathology, but also to the normal physiology.

The emphasis is on the physiology of the individual, but this is no denial of the importance of the psychological influences, social milieu and other environmental factors. More data on all these components is absolutely essential to a better understanding of behaviour and its aberrations. This study concentrates on the former aspect.

The choice of subjects was influenced by the data which indicates that primary affective disorders are relatively discrete, in particular the bipolar form. Fairly good criteria exist for diagnosis. Genetic factors are apparently strong. Response to physical treatment is superior to any

other treatment in the field of psychiatry. This suggests a potent physiological contribution. In view of the above factors and of many investigations which suggest disturbed neurophysiology, this group of patients seem to be good subjects for physiological study. They are relatively homogeneous.

Factors which further influenced the study, and the methadology used, were the periodic nature of the condition, indeed its therapeutic reversability, and the possibility of seeing the same patient in two different clinical states. These two contrasting states, mania and depression, are both manifestations of the same disease. It was therefore possible to see the subjects in one and/or other illness phase and in a recovery phase. The subjects could then act as their own controls. This strategy has difficulties attendant upon it. Of particular interest is the matter of whether the chemical indices used would measure a trait factor rather than a state factor, in which case it could be difficult to see the pathological aspect, in view of normal controls not being used. Fortunately this did not prove to be a problem, in fact the strategy probably enhanced the incisiveness of the study as shifts could be seen for values lying for the most part within normal limits.

In the review of literature it can be seen that biogenic amines have been the subject of extensive study in primary affective disorders. It would be naive to think that such multifaceted behaviour disturbance is the result of a single biogenic amine pathology. The probability of complex neurophysiological changes being responsible for this condition is high. Noradrenergic functional pathology in primary affective disorder has many proponents, as indeed has serotonin. Both dopamine and acetylcholine have been rather neglected by researchers in this area. In view of the strong changes in motor behaviour attendant upon attacks of primary affective disorder, it was decided to investigate dopamine. From the review of literature it can be seen that fairly

compelling evidence exists for the involvement of dopamine in the regulation of motor behaviour. The view is that dopamine may contribute significantly to the motor component of a complex neurophysiological disturbance, possibly involving noradrenaline, acetylcholine and peptides amongst others.

Investigating dopamine is a difficult problem and is limited by the available technical facilities allowing only indirect measurements in vivo at present. A dopamine system readily available to indirect assessment is the prolactin regulating system. A set of challenges with dopamine enhancing and dopamine blocking substances was considered desirable in order to stress the system mildly. A number of values for prolactin both in an illness phase and in a recovery period were obtained. It was naively hypothesized that the depressed state would be associated with a hypodopaminergic condition and might therefore be reflected in elevated prolactin levels. On the other hand mania would be the inverse and prolactin levels could be expected to be low. The hypothesis was based in part on the tonic dopaminergic inhibitory control of prolactin secretion. This proved to be an oversimplification and indeed the entire hypothesis was inverted following the results obtained. Having looked at the dopamine regulation of prolactin in primary affective disorders the question is, can the findings be extrapolated to other central dopamine systems? When considering other evidence in relation to dopamine in primary affective disorders it seems possible that this may not be a purely local dopamine/prolactin aberration. Dopamine functions in other systems may also be altered in this group of patients.

It is hoped that this study may contribute a small amount of data to the larger pool. In time accumulation of data may allow a more cohesive and comprehensive understanding of the pathophysiology of primary affective disorders and possibly the physiology of behaviour.

CHAPTER 2

HISTORICAL REVIEW

PRIMARY AFFECTIVE DISORDERS

"....for sorwful ymagynacion is always hoolly in my mynde.... this melancholy and drede I have for dye, defaute of slepe and hevynesse hath sleyn my spirit of quycknesse that I have lost al lustihede (happiness)....I have suffered this eight yere and yet my boote (cure) is never the nere: for ther is phisicien but oon that may me hele...."

Chaucer 1372

2.1 ORIGINS

The history of madness is inextricably enmeshed with theology, demonology, witchcraft and folklore. Civilised societies of today still retain fragments of these beliefs while preliterate and transitional cultures, as can be seen in Africa, are steeped in mystical beliefs about madness. The cause of madness in these cultures may be related to the ancestors (amadlozi) having been angered. It is interesting to note that the European cultures have frequent references to states of lowered mood, and much literature has specific terms referring to depression (outlined later). There does not appear to be clarity of terminology in many of the African cultures where symptoms of depression are referred to rather than a more specific "nosological" term, for instance, "my blood is cold" (igazi liya banda). European literature and folklore is replete with reference to melancholia, which is a very well developed concept.

2.2 GREEK CONCEPTS

Supernatural powers played a very important part in madness in early Greek culture. Evil spirits which emanated from

"dread goddesses" such as goddess mania, could be sent by the angered gods. The "cult of the dead" is frequently seen in preliterate cultures (as in Africa) and was present in early Greek culture. The Greeks had cultural "treatment" rituals which were to appease the angered gods. Many African tribes also have clear cultural treatment rituals which are performed to pacify their displeased ancestors.

There was little attention paid to the legal status of the afflicted persons.

The physicians concerned with the medical treatment of psychiatric patients developed some fairly systematized ideas on treatment and mental illness. Hippocrates (Friedman and Kaplan,1967) in the 4th century B.C. wrote on the four humours - blood, black bile, yellow bile and phlegm. The temperament of a person was related to the dominance of a humour. The English derivates from these concepts are still with us today - sanguine, melancholic, choleric and phlegmatic! Since the 5th century B.C. the notion that the brain had an important function with the senses and intellect resulted in Hippocrates writing "...and by the same organ (the brain) we become mad and delirious, and fears and terrors assail us". He also said that "joys and delights" and "sorrows and grief and despondency" originated in the brain.

"Melaina chole" (black bile) is the origin of melancholia which is still in use today. Melancholia unmistakably refers to depressive conditions (affective disorders), which were thought to be caused by an excess of black bile. Treatment at that time was very poor, unless purgation could be considered a type of counter irritation! Bathing and diets were also frequently prescribed.

2.3 ROMAN INFLUENCES

The Romans were influenced by the Greek concepts and the great physician Galen (Friedman and Kaplan, 1967) was particularly taken by the theory of the humours. Galen

devoted a considerable amount of time to melancholia, recognising the central position of despondency (dysthymia) and fear (anxiety). Description of sub-types flowed from his pen. Galen's concepts of health and disease were almost the "anlage" of our present theories of melancholia. The right balance of the humours (transmitters) were necessary for health. An excess of black bile "melaina chole" (perhaps acetylcholine) would give rise to a dreadful despondency (melancholia). It is only very recent research that is looking closely at an excess of cholinergic activity as being a factor in depression. This analogy may, of course, be entirely fortuitous - is it not closer to the truth than Freud's views on depressive illness? Galen believed that the treatment of melancholia was corrective education (psychotherapy).

At least two writers of the 1st century B.C. described mania. Asclepaedes recognised a state of excitement which was not associated with fever. It was continuous and unabating for considerable periods.

Aretaeus anticipated the great Kraepelin in describing melancholia which terminated in a state of excitement (mania). Here was an incipient concept of a unitary condition which could give rise to depression and excitement (manic depressive disorder).

Treatment by certain physicians had become more enlightened. Modification of the environment and the development of a relationship(s) could be prescribed.

2.4 MIDDLE AGES

The Middle Ages were not associated with remarkable developments in the field of affective disorders. Alexander of Tralles described a disorder of a circular type, which had alternating periods of melancholia and mania.

The entwinement of psychiatric disorders with religious attitudes and witchcraft do not allow for clear recognition of psychiatric conditions. Even the more rational and less superstitious physicians could hardly escape the idea that the devil must be lurking somewhere in the background. While Christian influences at this time were not always favourable, the Moslem influence in Arabia led to a much more humanitarian approach to the mentally ill. The Moslem belief that the insane may be closer to God, or favoured by him, was responsible for this sobering effect.

2.5 LITERARY CONTRIBUTION

European literature during this period dealt with the condition of man. The presenting quotation of this work is derived from Chaucer "....for sorwful ymagynacion is always hoolly in my mynde....this melancholye and drede I have for dye, defaute of slepe and hevynesse hath sleyn my spirit of quycknesse that I have lost al lustihede (happiness)....I have suffered this eight yere and yet my boote (cure) is never the nere: for ther is phisicien but oon that may me hele...."

It can be assumed that such a remarkable description of the phenomenology of a depressive episode could only have been the product of a sufferer from the condition!

William Shakespeare wrote profusely on the plight of people in a literary manner of their "psychiatric" status. Hamlet appears to have had considerable mood disturbance as reflected in his quotation:-

"O, that this too, too solid flesh would melt, thaw and resolve itself into dew! Or that the everlasting had not fix'd his canon 'gainst self-slaughter! O God! How weary, stale, flat and unprofitable seem to me all the uses of this world. Fie on't. O, fie! 'Tis an weeded garden that grows to seed; things rank and gross in nature possess it merely."

In his discussion on melancholy Burton (1932) made the following remarks:-

"In disposition, is that transitory melancholy which goes and comes upon every small occasion of sorrow, need, sickness, trouble, fear, grief, passion and perturbation of the mind, any manner of care, discontent, and vexation of spirit, any ways opposite to pleasure, mirth, joy, delight, causing forwardness in us, or a dislike!"

Burton (1932) also discusses the species or kinds of melancholy and quotes Hippocrates as agreeing basically on three types of melancholy; the first being from the brain - head melancholy; the second from the whole body; and the third from the bowels, liver, spleen or membrane called the mesenterium. The latter type is a hypochondriacal depression. Whether the difference between the first and second is a reactive/endogenous distinction is not clear. Certainly the second type seems to be somatized or vitalised depression.

Burton quotes a number of authors who support the theory that old age increases the risk of depression. He believed it to run in families. "it being an hereditary disease".

He covers a wide variety of "etiological factors", from bad diet and bad air to excessive exercise, enforced solitariness and bad marriages.

2.6 THE ORIGINS OF SCIENTIFIC PSYCHIATRY

The 19th century German organic school of psychiatry which, in my view, has contributed so much, was influenced by Thomas Aquinas (Friedman and Kaplan, 1967) who entrenched the organic and somatic approach. He rejected the concept of the soul being involved in "psychiatric" disorder, and laid the foundation for organic psychiatry. Melancholia and pathological anger (possibly mania) were decribed by Thomas Aquinas.

Another important development was to follow Sydenham (Friedman and Kaplan, 1967), whose descriptive approach produced the thrust for 17th and 18th century descriptive psychiatry.

An interesting discussion on mania by William Cullen in the 18th century focuses on two interesting aspects; firstly, he considered that mania was the result of a disorder affecting the brain, and that some "energy imbalance" in the nervous system could be involved in its causation and secondly, the treatment recommended was sedation with opium.

Here is evidence of an early attempt at rational psychopharmacological intervention. While this was not the first pharmacological therapy it had rational grounds. It is known that the use of extracts of Rauwolfia Serpentina had been used in preliterate times in India, to control behaviourally disordered people. The subsequent identification of reserpine as the active ingredient has contributed to our understanding of brain function (Bowman and Rand, 1980).

2.7 THE ORGANIC SCHOOL

It was against this 17th and 18th century development that Kraepelin (1921) made his contribution. He was extensively schooled in the "organics" of the nervous system, while being somewhat limited in his social view of behaviour. This heavily organic, and patient orientated view, combined with the extensive collection of relevant data, culminated in a major step in psychiatry; the clear unification of melancholia and mania into the manic depressive psychosis and its separation from schizophrenia (dementia praecox).

While Kraepelin's contribution may not have been appreciated by American psychiatry, which to its folly followed a contemporary of Kraepelin's (Sigmund Freud), Europeans continued their interests in organic psychiatry. Investigation into body form and temperaments/psychiatric illness was led by Kretschmer (Slater and Roth, 1969). His prototypes are well known and of relevance, the pyknic type was thought to

be extroverted, cyclothymic and even manic depressive. Sheldon (Slater and Roth, 1969) did a similar study, but his terminology was somewhat different.

2.8 AFFECTIVE DISORDERS

The term "affective disorders" has become an accepted term incorporating many conditions where depression (and, by some authors, - anxiety) is part of the central theme. Its usefulness is in allowing a large number of both minor and major conditions with significant mood change to be considered together. The biological sub-group of the affective disorders is usually referred to as the primary affective disorder being the group which is now under consideration.

The Kraepelinian view that all major depressive conditions could be subsumed under the heading of "manic depressive psychoses", has been considerably refined in the last three decades.

2.8.1 Bipolar and Unipolar

There is now some compelling evidence that at least two sub-groups of primary affective disorder exist, the bipolar and unipolar. The distinction is supported by evidence from Perris (1969), Gershon et al, (1979).

These are but a few of the genetic studies referred to later. Other approaches to this problem have been the investigation of biochemistry, treatment response, and the course of the condition. At present there is considerable theoretical support and practical usefulness in the bipolar/unipolar distinction.

Attempts at further sub-division into bipolar I and bipolar II (Dunner et al, 1976) seem to be both premature and not very useful. The relationship of affective disorders to schizophrenia remains a difficult one.

2.8.2. Schizo-affective

Kasanin (1933) introduced the term schizo-affective in attempting to deal with the interface between schizophrenia and manic depressive illness. Leonhard was also involved in this difficult area in his studies of atypical psychoses. These are matters that need further clarification. Although Pope and Lapinsky (1978) have drawn attention (rightly so, especially in the U.S.A.) to the probable misdiagnosis of manic depressives as schizophrenics, they have not materially contributed to the understanding of the relationship between schizophrenia and bipolar primary affective disorder.

2.8.3. Reactive/Neurotic - Endogenous Distinction

The relationship between reactive depression and pathological (endogenous) depression remains another difficult area; while at the extremes of the clinical picture of endogenous and reactive depression the distinction is clearly valid and useful, there is an enormous blur between these two poles. Aubrey Lewis (1938) argues that depressive illness is a continuum from mild to severe. Kendall (1976) has supported this view that the spectrum is from mild/chronic to acute psychotic depressive states.

Whatever the theoretical truth may be, the practical issue is clear. Those patients with endogenous symptomatology will respond better to physical and pharmacological treatment with antidepressant agents.

2.8.4. Convulsive Therapy

The introduction by Meduna (1935) of convulsive therapy has been a major stride in psychiatric treatment which has since been modified by the introduction of electrical induction (Ugo Cerletti 1938); the use of anaesthesia and skeletal muscle relaxants; and the refinement of equipment and indications. Convulsive treatment of primary affective

disorders remains the most effective intervention for the present attack, and may often be life saving (Kendall 1981).

2.8.5 Pharmacological Advances

The last three decades have seen unprecedented development in the field of psychopharmacology.

The introduction of imipramine and chlorpromazine in the mid-nineteen fifties saw the beginning of a revolution in the treatment of severe psychiatric disorders.

Affective disorders have benefited from an expansion of available antidepressants, the second generation drugs having good efficacy with less side effects. The management of mania has become far more effective with the use of neuroleptics such as chlorpromazine and haloperidol, and the use of lithium carbonate (Cade 1949). Lithium has undoubtedly been a major advance as it is most useful as a prophylactic agent.

The recognition that monoamine oxidase inhibitors have the capacity to reverse depressive states, emerged from the early treatment of tuberculosis. These drugs remain a useful part of the armamentarium of managing primary affective disorders.

Modern pharmacology has had a profound effect on behavioural science. The understanding of drug action and its ability to penetrate brain and behaviour, should come as no surpise. As a result of a wide variety of experimental and therapeutic psychopharmacological and biochemical techniques, we stand at the brink of a new understanding of behaviour. It is hoped that this work might contribute a small amount to this body of evidence.

2.8.7 Social Data

Finally the era of social data has broken upon us with Brown

(1978), and others, collecting objective data on the influence of environment, such as the family and life events on the course of depressive illness.

No review has been made of the psychotherapeutic aspects of primary affective disorders, as it is with the organic aspects of primary affective disorders that this investigation is concerned. It is considered that psychotherapy is outside of the scope of this review.

CHAPTER 3

LITERATURE REVIEW

3.1 GENETICS AND PRIMARY AFFECTIVE DISORDERS

Genetic factors play a vital role in the production of a vulnerability to primary affective disorders. This fact increases the probability that investigation of nervous system function will find some biochemical deviation in this illness.

The evidence that genetic factors play an important role in primary affective disorders is unequivocal today, and is accepted by all experts working in this field. The problems that remain relate to the mode of inheritance, and to the homogeneity of the primary affective disorders.

Most of the genetic work has relied on twins studies as well as adoptive and family studies. No attempt will be made to review all the literature, only a short summary of the important findings will be given.

Pooled data from seven twin studies in affective disorders give overall concordance rates of 76% in monozygotic twins, contrasting with concordance rates of 19% in dizygotic twins, (Rosanoff et al, 1935, Kallman 1942, Slater and Roth, 1969, Tsuang, M.T. 1975).

The concordance rates are not materially altered by the rearing apart of monozygotic twins! This is a profound finding (Price 1968).

Genetic linkage studies are still advancing. Claims by Winokur of X-linkage (using X-ga blood group and colour blindness as markers) have complicated the picture as to the mode of inheritiance. Winokur found a striking lack of ill-father/

ill-son pairs in the families he studied (Winokur and Tana 1969). Other studies have not, however, supported this view fully and reports of ill-father/ill-son are well documented (Perris 1973).

Evidence suggestive of some cases of X-linkage, or X-association, does exist. There may, however, be more than one gene involved in the inheritance of this condition.

Angst (1966) and Slater (1969), and others, suggest a single-autosomal dominant gene of reduced penetrance as the most likely mode of inheritance.

The question of heterogeneity has been under investigation. There is some evidence that at least two sub-types of primary affective disorders exist - (a) the bipolar type, and (b) the unipolar type. These two types appear to breed true with insignificant risk of unipolars arising from bipolar stock, or bipolars arising from unipolar stock (Perris 1966).

On a broad front no documented cases exist where one member of a monozygotic twin pair has a different psychosis from the other, excluding those single twin members who may have suffered an event, for instance, brain damage. Cohen (1972) conducted a study of 260 pairs of twins who had presented with manic depressive illness (40), schizophrenia (194) and schizo-affective disorders (26). No single case was reported where the type of psychoses differed in a monozygotic twin pair.

The risk of primary affective disorders in the general population is about 1%. The risk to a first degree relative is about ten-fold this figure (Zerbin-Rübin 1961).

There is abundant evidence for powerful genetic factors producing vulnerability to primary affective disorders. The challenge that flows from this information is, how does the genetic factor influence the chemistry and physiology and, what is the interaction between organic vulnerability and environmental influences?

3.2 RELEVANT PHYSIOLOGICAL AND PHARMACOLOGICAL FACTORS

The organic aspects in primary affective disorders relevant to this study will be reviewed from the literature. The short overview of genetics merely underscores the importance of these organic components. The review will include a wide variety of approaches, which may have bearing on the functions under investigation. Work on intracranial self-stimulation is included as it is involved with the catecholamine systems and is heavily influenced by psychoactive drugs used in primary affective disorders.

3.3 DOPAMINERGIC SYSTEMS OF THE BRAIN

3.3.1 The Mesotelencephalic Dopaminergic System

3.3.1.1 The Mesolimbic System

The dopaminergic cells of the mesolimbic system lie in the ventral tegmental area A.10 (Fig. 1 & 2). A small amount of innervation also arises from the cells in area A.9 (van Rooyen 1980). These neurones terminate on a number of limbic structures:-

a) the nucleus accumbens septi;

b) the amygdala and septum;

c) the olfactory tubercle;

d) The interstitial nucleus of the stria terminalis.

3.3.1.2 The Mesocortical System

The neurones of the mesocortical system reside in area A.9 and A.10 (Fig. 1 & 2) and are distributed to the frontal cortex and the cingulate gyrus. Projections also occur to the suprarhinal and ventral entorhinal cortex and antero-medial cortex (van Rooyen 1980).

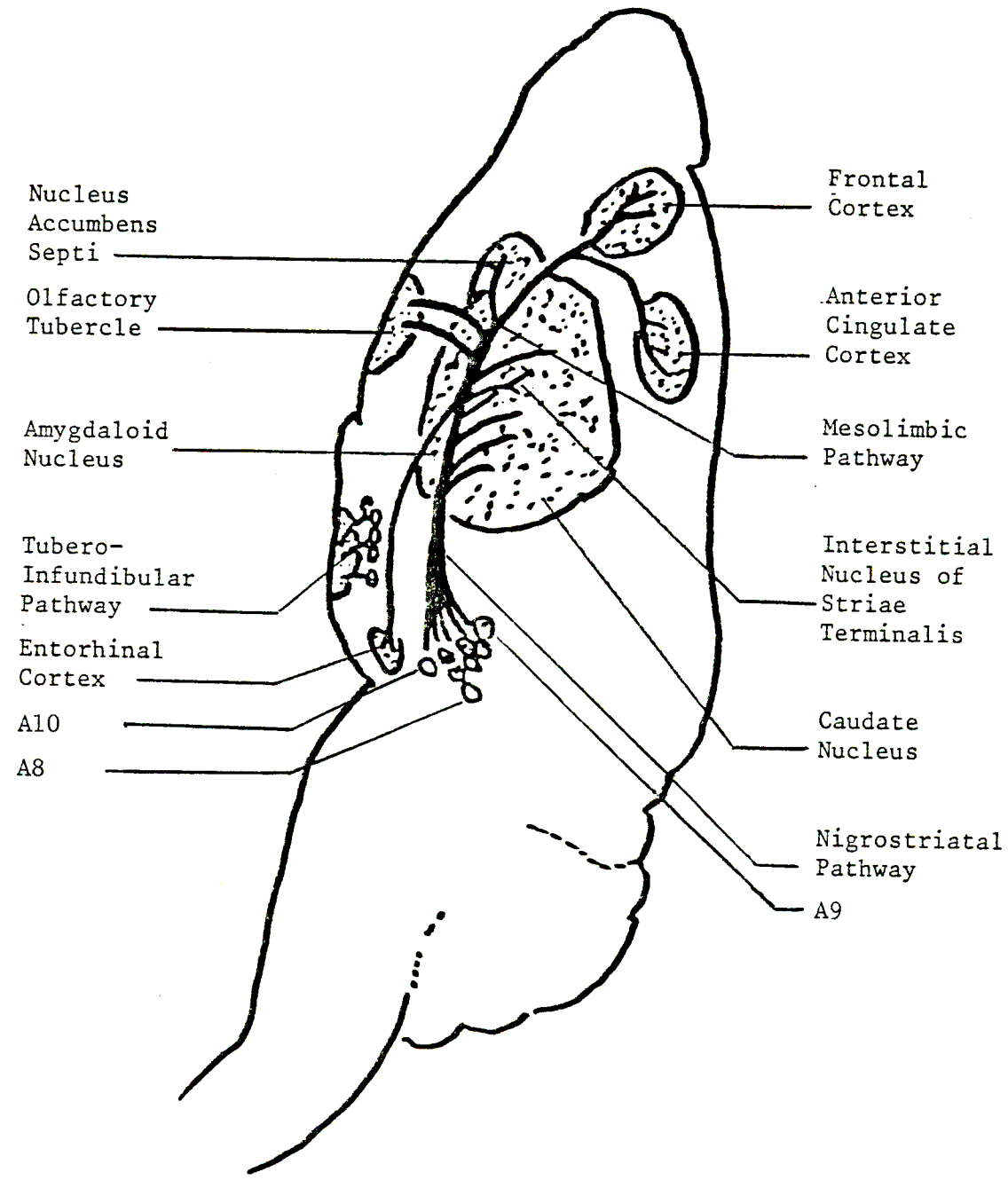

FIG.1 DOPAMINERGIC SYSTEMS

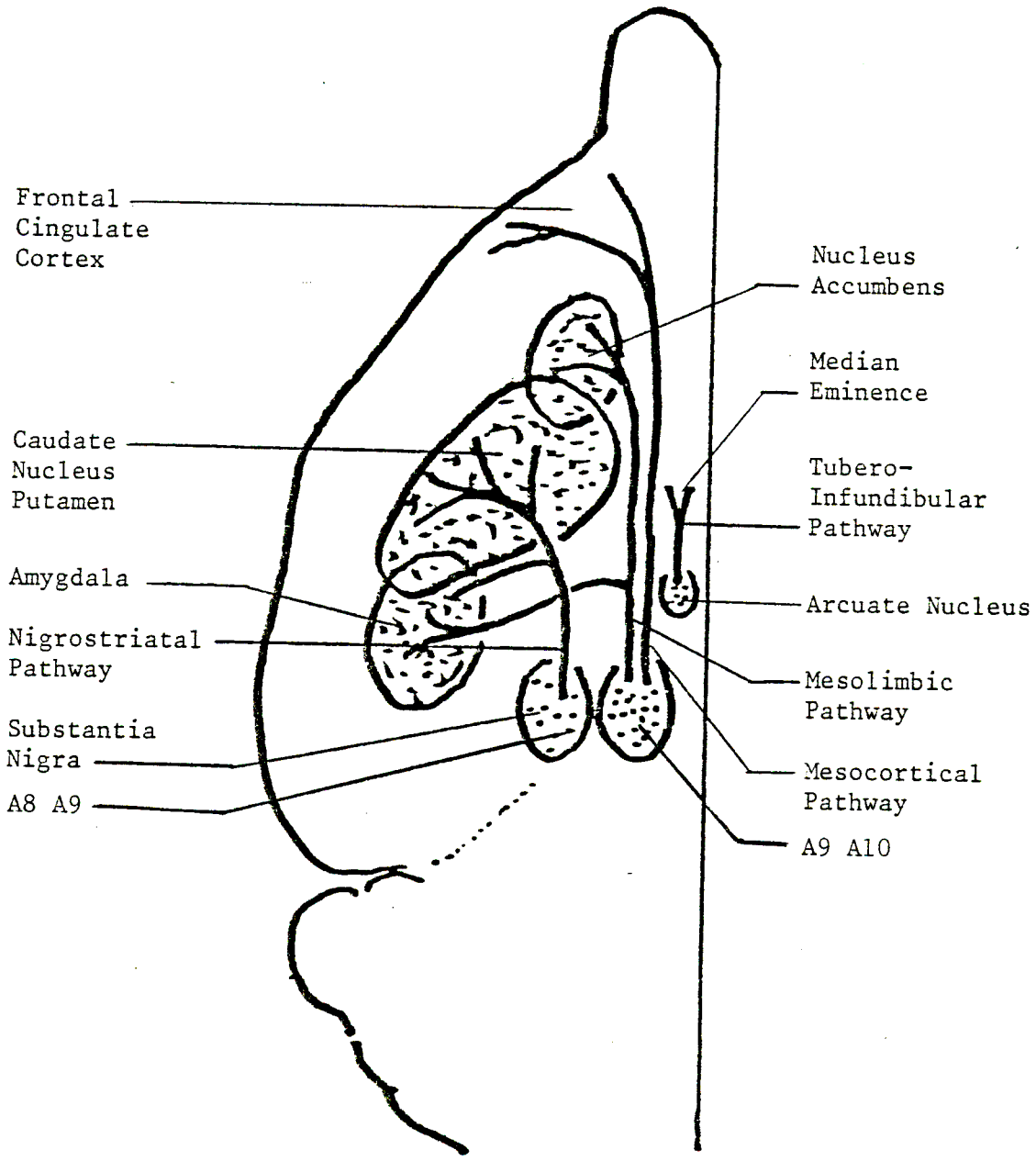

FIG.2 DOPAMINERGIC SYSTEMS

3.3.1.3 The Nigrostriatal Dopaminergic System

The cell bodies in this system lie in the substantia nigra, area A.8 and A.9 and terminate in the neostriatum Fig. 1 & 2) (Dahlström and Fuxe, 1964).

3.3.2 Hypothalmic Dopaminergic Systems

3.3.2.1 The Tuberohypophyseal Systems

This system projects to the median eminence, neural lobe and pars intermedia of the hypophysis (Fig. 1 & 2). The cell bodies lie in the arcuate A.12 and periventricular nucleii. Many of the terminals in the median eminence are packed against the portal system. The system releases dopamine into the portal vessels carrying it to the anterior pituitary (Bjorklund et al, 1970).

This is not a complete review of the dopaminergic systems, but is restricted to those systems which are thought to be relevant to motor function and motivation. The tuberohypophyseal system is included, as it constitutes the experimental system, which may reflect possible changes in the motor dopaminergic systems.

3.3.3 Other Dopaminergic Systems

a) the incertohypothalmic system;

b) the periventricular system;

c) the periglomerular dopaminergic neurones;

d) the retinal system;

e) the chemo-emetic trigger system.

3.4 DOPAMINE RECEPTORS

3.4.1 Non-Adenylate Cyclase Associated Dopamine Receptors And Receptors Negatively Regulating Adenylate Cyclase

3.4.1.1 Dopamine 2 Receptors (D_2)

The D_2 receptors are non-adenylate cyclase dependent receptors (Kebabian and Calne, 1979). Physiological concentrations of dopamine at the micromolar level exerts influence on these receptors. Therapeutic levels of antipsychotic agents at nanomolar levels block these receptors.

The distribution of the D_2 receptors is in the following dopamine systems:-

a) the nigrostriatal system;

b) the mesolimbic system;

c) the hypophyseal system. (There appear to be both D_2 and D_4 receptors present).

d) the chemo-emetic trigger zone.

Increased numbers of D_2 receptors have been reported in schizophrenics at post mortem, particularly in the limbic area. This is reported in both treated and untreated patients. Studies show that micromolar concentration of dopamine and nanomolar concentrations of antipsychotic agents, are liable to displace radioligands from these receptors. The evidence is reasonably clear that this is the receptor site of action of the antipsychotic agents (Walters 1983).

3.4.1.2 Dopamine Receptors on Pituitary Mammotrophs (D_4)

According to Kebabian (1978) the mammotrophs in the adenohypophysis have D_2 like receptors which do not regulate adenylate cyclase. The receptors appear to be extremely sensitive, responding to concentrations of dopamine in the namomolar range (2 - 4 nanomolar). These are the concentrations of dopamine which are physiologically concerned with the inhibition of prolactin. The agonists ^{3}H-apomorphine and ^{3}H-ergot are used as ligands for these receptors (Walters 1983). The concentrations of antipsychotic agents to

which these receptors respond are nanomolar, that is, therapeutic levels. More recently a number of workers have reported D_2 receptors negatively regulating adenylate cyclase. Giannattasio and co-workers (1981) reported dopamine receptors in the anterior pituitary of female rats which inhibited adenylate cyclase. They believe that these receptors show pharmacological similarities to the prolactin inhibiting receptors.

Apparently the female rat anterior pituitary contains the relevant cells in far greater numbers than the male rat pituitary, which failed to demonstrate significant adenylate cyclase inhibition.

These researchers have also produced evidence that this inhibory effect of dopamine on adenylate cyclase is entirely dependent on guanosine-5-triphosphate. Cote and co-workers (1982) support the dependence of adenylate cyclase inhibition on guanosine-5-triphosphate. Their study was conducted on the intermediate lobe of pituitary in relation to the synthesis and secretion of alpha-melanocyte stimulating hormone. It therefore appears that dopamine receptors of D_2 type exist in the anterior and intermediate lobes of the pituitary. The inhibition of adenylate cyclase by these receptors is dependent on guanosine-5-triphosphate. In the anterior pituitary they probably play a part in the inhibition of prolactin secretion.

Stoof and Kebabian (1981) demonstrated D_2 dopamine receptors in the neostriatum of the rat which are negatively linked to adenylate cyclase. It appears therefore that there may be D_1 and D_2 receptors in the neostriatum with opposing roles mediated by their contrasting effects on adenylate cyclase.

3.4.1.3 Dopamine 3 Receptors - Autoreceptors (D_3)

Another group of receptors, D_3, which do not regulate adenylate cyclase are the autoreceptors. A significant proportion of these receptors are presynaptic in their location, for instance on the dopamine neurone terminals. These D_3 receptors

control of negative feedback loop on dopamine synthesis and release. These receptors are sensitive to nanomolar concentration of dopamine, which is considerably lower than the concentration to which D_1 and D_2 are sensitive. It is possible to obtain selective agonistic activity by apomorphine at the D_3 receptor site (pre-synaptic non-adenylate cyclase dependent system). The concentration of most antipsychotic agents to which D_3 receptors are sensitive are in the micromolar range. When low concentrations (nanomolar) of apomorphine are used the behavioural effect is one of lethargy and sedation, due to the differential effect on D_3 receptors. When higher concentrations are used, the D_2 receptors are involved, the animal shows increased locomotor activity (Meltzer 1982) due to predominant effects on these post-synaptic dopamine receptors.

3.4.2 Dopamine Receptors Positively Regulating Adenylate Cyclase (D_1)

Dopamine and 2-amino-6, 7-dihydroxy-1,2,3,4,-tetrahydronaphthalone are full agonists on adenylate cyclase linked dopamine receptors, while apomorphine is a partial agonist. Micromolar range of agonists are required for the stimulation of dopamine sensitive adenylate cyclase (EC50's e.g., dopamine 2×10^{-6}, 2-amino-6,7,-dihydroxy-1,2,3,4,-tetrahydronapthalone 4×1^{-6} and apomorphine 2×10^{-6}). The value as seen here for dopamine is at physiological levels (Kebabian et al, 1975).

The concentration of antagonists necessary to inhibit dopamine sensitive adenylate cyclase is supra-therapeutic (IC50's are around 6×10^{-7}). The neuroleptics in plasma are in the nanomolar range. These substances are, therefore, weak inhibitors of dopamine sensitive adenylate cyclase (Walters 1983).

3.5 DOPAMINE SYNTHESIS

The synthesis of dopamine occurs in the axon of the dopamine

Synthesis of catecholamines

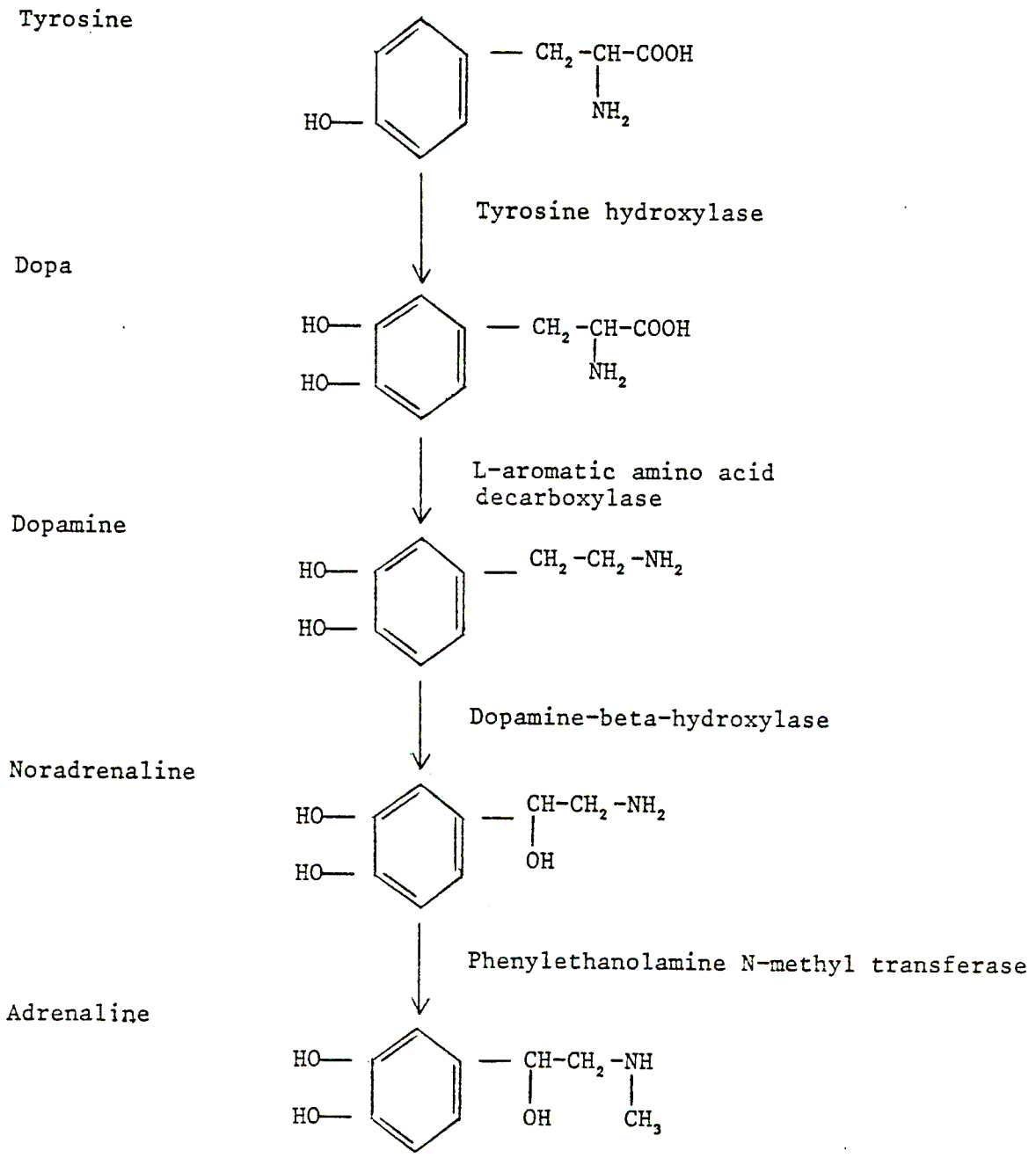

FIG.3 DOPAMINE SYNTHESIS

neurone and is transported to the nerve terminals where it is stored in two forms - the protein bound granular form (in vesicles) and a non-granular form (Blaschko 1953). The storage system in vesicles consists of both stable and labile components.

3.6 DOPAMINERGIC SYSTEMS AND BEHAVIOUR

Fundamental to the theoretical construct of this study is the position of dopamine in relation to motor behaviour. Part of the evidence will be reviewed here, the remainder is dealt with in the appropriate sections.

Manipulation of dopaminergic function by various pharmacological agents and strategic combination of agents, together with lesioning experiments has produced some enlightening information.

The action of amphetamines, as dicusssed in more detail elsewhere, is via dopamine and noradrenaline. Low doses of amphetamines (1mg./kg. body weight) produces motor arousal, i.e. exploratory running behaviour, which is well integrated (Ungerstedt and Ljunberg, 1973).

High doses of amphetamines (5-10mg./kg.) produce high frequency repetitive brief "snatches" of behaviour; at first grooming repeatedly and later stereotyped sniffing at high frequency.

Treatment with alpha-methyl-para-tyrosine is associated with attenuation of these motor phenomena. The nigrostriatal system is known to be damaged in Parkinson's disease, where there is relative akinesia (lack of initiation of movement) as well as rigidity and tremor. L-dihydroxyphenylalanine improves these symptoms. Injection of 6-hydroxydopamine into the substantia nigra bilaterally, produces a profound loss of dopamine in this system. Where extreme loss of dopamine occurs motor arrest is seen (lack of initiation of

movement). High doses of amphetamine fail to produce stereotyped behaviour in these animals. The rapidly repeated stereotyped behaviour is, therefore, thought to be related to nigrostriatal hyperactivation where the new movement begins before the preceding sequence is completed. Low doses of amphetamine are, however, able to produce behavioural arousal, exploratory running in these animals! This suggests that motor arousal, or the driving of motor behaviour, is from a different source and that the substantia nigra is involved in the execution of motor behaviour. This is further evidenced by the asymetrical effects on motor activity of unilateral lesions of the substantia nigra. Stimulation of motor activity under these circumstances produces rotational asymetry; amphetamine causing rotation towards the side of the lesion and apomorphine producing rotation away from the lesion. The latter effect is due to dopamine receptor supersensitivity in the damaged system.

The mesolimbic system has been similarly studied. Lesions of the nucleus accumbens septi produce distinctly different effects from those of the substantia nigra. Low doses of amphetamines fail to produce motor arousal following lesions of the nucleus accumbens septi (Kelly et al, 1975). It is possible, however, in this preparation to illicit stereotypy on high doses of amphetamines, the nigrostriatal system being intact. The local injection of dopamine, amphetamine, or apomorphine into the nucleus accumbens septi leads to a relatively short lived, but distinct increase of locomotor activity (Pijnenberg et al, 1976). This effect can be incisively blocked by local injection of haloperidol (Cools 1977). Apomorphine is a full agonist at the D_2 receptors and a partial agonist in the D_1 receptors.

Bromocriptine is also a dopamine agonist and increases locomotor activity in animals (Corrodi et al, 1973) and it does not stimulate adenylate cyclase (Fuxe 1978). This again suggests that the receptor responsible for increased locomotor activity is a D_2 receptor.

The increase of locomotor activity produced by apomorphine in normal animals is not as well integrated as is the enhanced locomotor activity produced by amphetamines (Ungerstedt and Ljunberg, 1973). The level of locomotor activity is also greater with amphetamines. The addition of clonidine to apomorphine increased the level of locomotor activity (Maj et al, 1972) and its integration to approximately that produced by amphetamines. The locomotor activity effects of apomorphine are blocked by the local injection into the nucleus accumbens septi or parenteral administration of neuroleptics. The neuroleptics at normal therapeutic doses appear to be acting on the D_2 receptors, rather than the D_1 receptors (Cools and van Rossum, 1976).

Rotational effects of unilateral nigrostriatal lesions are modified by stimulation of the nucleus accumbens septi. It is the rate of rotation that is increased by nucleus accumbens septi stimulation, but unilateral stimulation of the nucleus accumbens septi does not affect the direction of rotation. This is further evidence suggesting that the nucleus accumbens septi instructs or drives behaviour and may influence its rate, but not its pattern of execution (Iversen 1977).

Bilateral injections of the D_1 receptor antagonists (ergometrine) into the nucleus accumbens septi, leads to a more sustained increase in locomotor activity after a latency of about thirty minutes. This effect can be inhibited by the local injection of dopamine.

The apparently reversed effect is probably due to the action of these drugs on different receptors. Increased locomotor activity may result, therefore, from dopamine agonists on D_2 receptors in the nucleus accumbens septi or by blocking D_1 receptors with ergometrine injected locally into the nucleus accumbens septi (Cools 1977).

It appears that there may be a complex self-modulation of dopamine, which effect is dependent on a different receptor

from that which drives behaviour.

Mesolimbic structures support high rates of intracranial self-stimulation as discussed later.

Enhancement of dopamine activity by direct, or indirect agonists has been reported to induce "psychosis" and to precipitate mania in patients (Goodwin et al, 1971, Post 1975, Parkes 1979). Substances used in the treatment of primary affective disorders, the first and second generation antidepressants and monoamine oxidase inhibitors have also been reported to promote mania. This information is important in the management of primary affective disorders because both antidepressants and/or the neuroleptics may increase the "swinging" of bipolar patients.

Lesions of nucleus accumbens septi attenuate the increased locomotor activity produced by drugs acting directly, or indirectly, on the dopamine receptors. Evidence of the interaction between noradrenaline and dopamine has also been cited.

Ljunberg and Ungerstedt (1973) demonstrated that lesions of the ventral noradrenergic bundle interfered with learning. This role of noradrenaline in relation to dopamine has also been investigated by Iversen and Frey (1980), amphetamines enhancing learning and behavioural efficiency.

Lesions of the ventral tegmental area certainly regularly disturb behaviour and interfere with learning and behavioural efficiency. Forebrain release of dopamine seems to be necessary for focusing and attending to environmental stimuli. Tassim et al, (1979) demonstrated that lesions of noradrenergic ascending pathways reduced the levels of turnover of dopamine in the ventral tegmental and cortico-limbic areas.

Noradrenaline has long been implicated in stress and the dialogue between noradrenaline and dopamine is probably involved

in adaptive behaviour. It would indeed be surprising if this was not so.

Noradrenaline appears to be important in learning effects, bilateral lesions of the locus coeruleus is not associated with reduced rates of running in a maze, but with impaired learning. These noradrenergic systems seem to be responsible for the "reinforcing" effects on behaviour. This reinforcement is presumably contingent upon bio-socially successful behaviour.

3.7 NORADRENERGIC SYSTEM IN BEHAVIOUR

3.7.1 The Anatomy of Noradrenergic Systems

3.7.1.1 The Ventral Noradrenergic System

The cell bodies of the ventral noradrenergic system lie in a number of cell groups in the pons and medulla. The ventral noradrenergic system runs to the hypothalamus (Fig. 4 & 5).

3.7.1.2 The Dorsal Noradrenergic System

The cell bodies of the dorsal noradrenergic system are located in the locus coeruleus and the fibres run into the Purkinjie cells of the cerebellum (inhibitory), and to the frontal cerebral cortex and the pyramidal cells of the hippocampus. Noradrenergic innovation of limbic and cortical sites is, at least in part, concerned with aspects of associative learning (Kety 1970) (Fig. 4 & 5).

3.7.2 Function of the Noradrenergic Systems

The release of noradrenaline is associated with reinforcement and facilitation of learning and memory (Gray 1977). Gray has produced evidence that for rats to be able to show the partial reinforcement effect, the dorsal noradrenergic bundle must be intact. If this is correct, the noradrenergic system may be responsible for learning, and the reinforcement

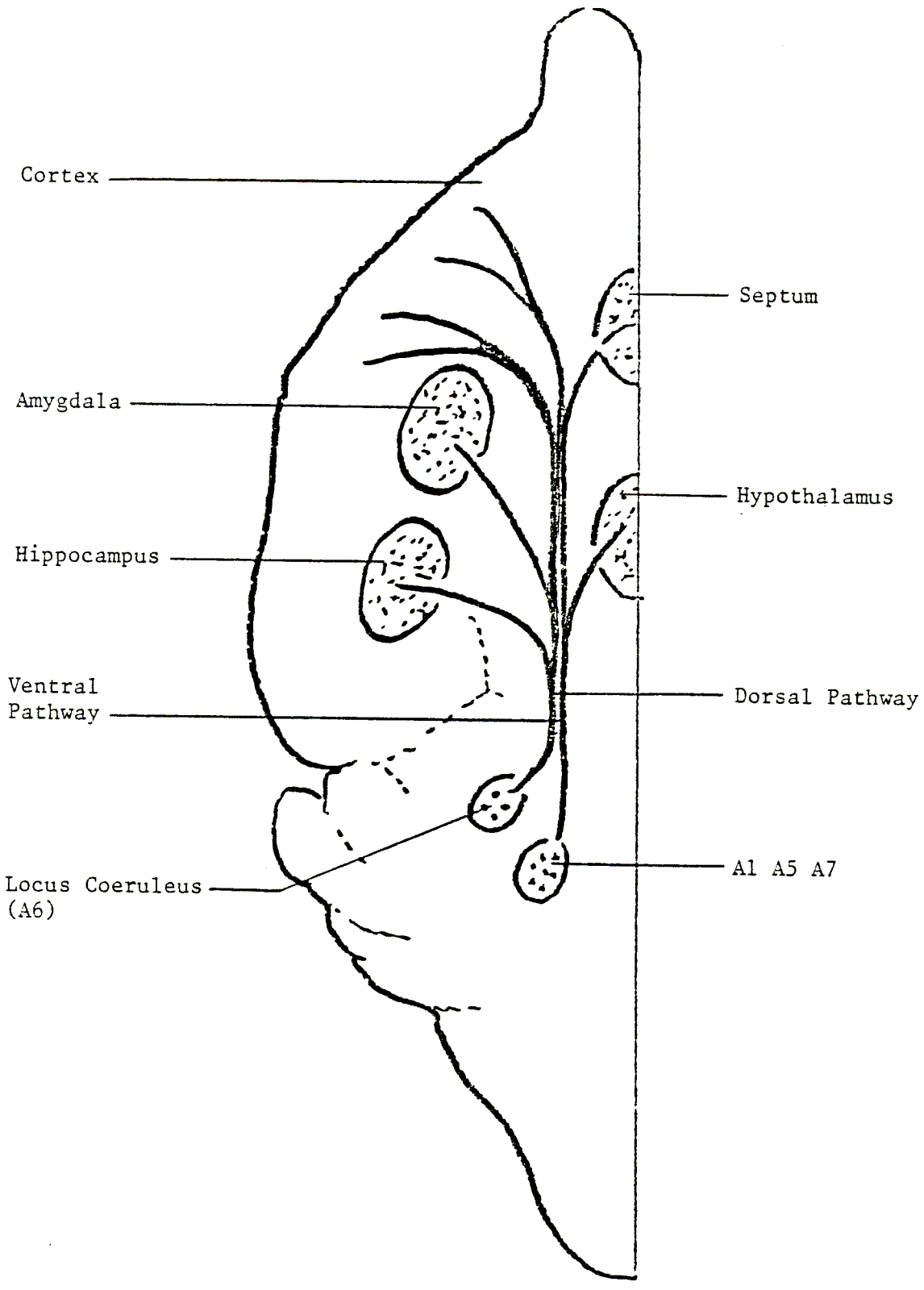

FIG. 4 NORADRENERGIC SYSTEMS

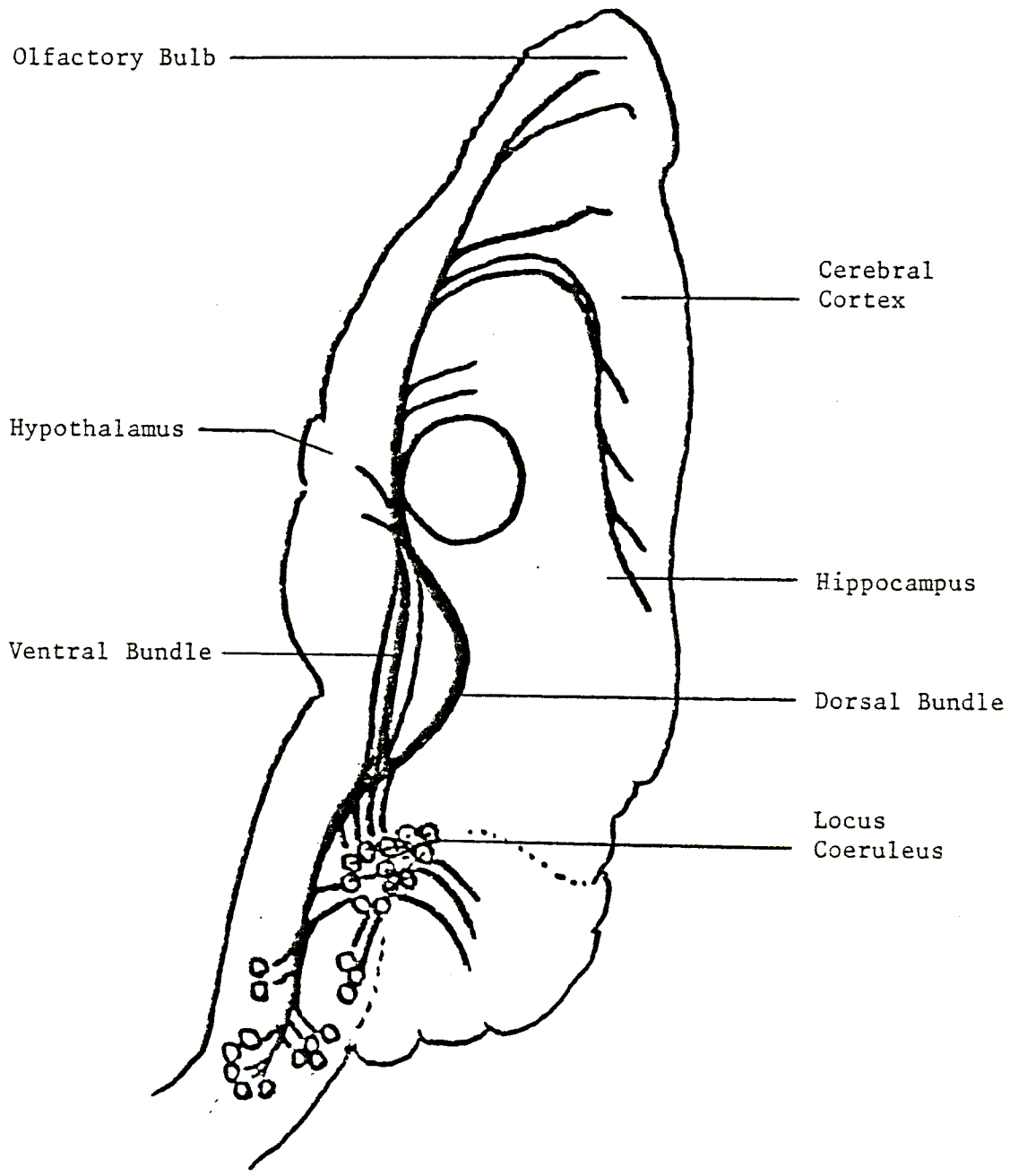

FIG.5 NORADRENERGIC SYSTEMS

of bio-socially successful behaviour, which is driven and executed by dopaminergic systems. This makes noradrenaline a very good candidate for mood regulation, in particular a feeling of well-being (mood-elevation), as this is contingent upon bio-social success and presumably reinforcement.

Further evidence of interaction between noradrenaline ascending pathways and dopamine in areas innervated by dopaminergic cells from A.10 has been produced (Tassim et al, 1979). Lesions of the ascending noradrenergic bundles resulted in reduction of dopamine in the areas of distribution on dopamine neurones from Area A.10. Noradrenaline exerted some facilitatory influence on the dopamine neurones. Further support for this is offered by the enhancing effect of clonidine on apomorphine in locomotor activity, again suggesting an interaction of the noradrenergic systems on dopaminergic systems.

It is, of course, possible that just such an interaction is the basis of the experience of mood enhancement. Further, locomotor activity produced by amphetamine is greater than that produced by apomorphine alone. This suggest that amphetamine, having effects on both dopamine and noradrenaline displays an enhancing effect on dopaminergic function; we also know that amphetamine enhances mood! Mason and Iversen (1979) have, however, produced evidence, which at least in part, contradicts this view and it seems that further elucidation must be awaited (Mason and Iversen, 1979).

The problems associated with lesioning experiments are numerous. It is, therefore, vital that confirmation of all work is obtained, preferably from more than one source.

3.7.3 Lesions of Transmitter Pathways

Selective lesioning, e.g. by electrolytic technique or radio lesions are not specific enough. 6-hydroxydopamine destroys catechalamines containing neurones. Another problem is the completeness of the lesion, for instance, one may get

partial lesions. Other problems associated with lesions are:-

a) increased turnover by surviving neurones;

b) higher electrical activity of the surviving neurones;

c) receptor responses may be increased.

Re-growth is also found in the catecholamine systems with collateral growth (Raisman 1969, Mason and Koob, 1978).

Noradrenergic involvement in attention has also been mooted, but requires further testing. This would certainly be congruent with the ideas just considered.

3.8 PSYCHOTROPIC AGENTS, CATECHOLAMINES AND PRIMARY AFFECTIVE DISORDERS

A review of psychoactive agents which affect primary affective disorders and catecholamines is of great interest and relevance. Substances which alter the functional state of the brain catecholamine systems and modify illness phases of primary affective disorders throw light on the pathophysiology of this condition. A number of substances are reviewed which are effective in altering the illness phase of primary affective disorders. Other substances appear to be active in modifying the functional state of the catecholamine systems whether normal or pathological. Correlations between mechanisms of action and therapeutic and experimental effects in normal and ill subjects are referred to. These have yielded a wealth of circumstantial evidence about the physiology of normal and abnormal behaviour.

This study is concerned with the possible role of dopamine in affective disorders. The broader implication is also of great interest, that is the role of dopamine in normal motor activity. A discussion of dopamine will inevitably involve noradrenaline. The following sections deal in more detail with these issues.

3.8.1 Amphetamines and Related Drugs

The mechanisms of action of amphetamines is primarily on the catecholamines, acting indirectly on the dopaminergic and noradrenergic systems (Quinton and Halliwell, 1963). Increased amounts of dopamine and noradrenaline are made available at the receptor sites by releasing dopamine and noradrenaline from the extra granular neuronal pools. This effect can be attenuated by pre-treatment with alpha-methyl-para-tyrosine a tyrosine hydroxylase inhibitor. Amphetamines have also been shown to have a small amount of monoamine oxidase inhibiting, and monoamine reuptake blocking effects. Direct agonist activity has been mooted, but this seems to be insignificant.

3.8.1.1 Effects on Man

The effects of amphetamines on human subjects is to increase motor activity, to reduce appetite for food and to induce euphoria. There is evidence that certain patients with bipolar affective disorder respond with more euphoria to amphetamines than do other depressives. The elevation of mood may be an index of response to imipramine (Martin et al, 1971, Maas et al, 1972, Silberman et al, 1981).

There is suggestive evidence that amphetamines and appetite suppressants (stimulants) are likely to induce mania in a number of manic depressives (Gerner et al, 1976).

The chronic use of amphetamines (and other stimulants), particularly in increasing doses, is sometimes associated with a psychotic state, usually of a paranoid type. It appears that there is a difference in the effects of chronic abuse as compared with acute use of amphetamines (Post 1975). Amphetamines are associated with transient, and infrequently, with sustained improvement of mood in depressive patients.

The effects of amphetamines on locomotor activity in laboratory animals has been well documented. There is good

evidence that they exert their motor effects via the dopaminegic system(s). Direct application of amphetamines to certain dopaminergic systems will increase locomotor activity in animals. This is discussed in greater detail elsewhere.

The selective antagonist, pimozide, reduced the locomotor activity induced in animals by amphetamines. This substance is rather a specific dopamine antagonist, although it has a fair amount of anticholinergic activity.

3.8.2 Drugs Affecting Primary Affective Disorders

3.8.2.1 Tricyclic Antidepressants

A wide variety of tricyclic antidepressants are available and are efficacious in major depressive episodes of primary affective disorders. The effects of the antidepressants vary in the extent to which they act on noradrenaline, 5-hydroxytryptamine and dopamine, as well as other neurotransmitters. There are those tricyclics which predominantly affect catecholamines, in particular noradrenaline, and are effective in reversing the depressive syndrome in a significant proportion of patients (Daneman 1961). Desipramine is of particular interest due to its predominant action of noradrenaline reuptake. It is as efficacious as imipramine (Mindham 1979).

3.8.2.2 Monoamine Oxidase Inhibitors and Second Generation Antidepressants

The antidepressant actions of monoamine oxidase inhibitors is probably due to the inhibition of the enzyme monoamine oxidase. There is, therefore, a resultant increase in the amount of dopamine and noradrenaline available, which enhances the dopaminergic functions.

Bipolar patients may respond better to monoamine oxidase inhibitors than do unipolar patients. Precipitation of

mania may also occur with monomine oxidase inhibitors in vulnerable people.

Maprotiline is a tetracyclic antidepressant with a predominant effect on noradrenaline reuptake, and its efficacy in major depressive illness is similar to that of the standard antidepressants (Pinto et al, 1972).

Nomifensine, while being a new molecule, has a considerable amount of activity in common with tricyclics. It does, however, strongly affect dopamine reuptake as well as noradrenaline. The drug is inclined to produce insomnia and restlessness. The push on motor activity is of interest in the context of the present study in view of its dopaminergic activity. It has been shown to be an effective antidepressant, and to lower the levels of prolactin (McCawley 1979).

There have been claims that nomifensine is also effective in treating Parkinson's Disease, due to its dopaminergic activity (Parkes et al, 1977).

3.8.2.3 L-dihydroxyphenylalanine

Studies on L-dihyroxyphenylalanine in depression are still problematic, particularly earlier studies where doses of L-dihydroxyphenylalanine were clearly inadequate. A later study by Goodwin and his co-workers (1971) with higher dosage produced interesting results. Goodwin and co-workers (1971) found that those depressed patients treated with L-dihyroxyphenylalanine had an increase of motor activity, but mood did not appear to be significantly increased.

Patients with Parkinsonism have also been found to be less depressed after treatment with L-dihyroxyphenylalanine (Celesia and Wanaker, 1972). Mindham et al, (1976) have reported on the treatment of patients with Parkinson's Disease and the occurrence of psychiatry morbidity. They found paradoxically a higher incidence of depressive reactions, particularly when there had been previous episodes of depressive illness.

L-dihydroxyphenylalanine is associated with increased incidence of mania and hypomania if given in doses in the region of 4gm. per day or 400mg. per day with a decarboxylase inhibitor. The risk of a manic attack while on treatment with L-dihydroxyphenylalanine is much increased if there is a history of previous manic attacks. The risk of mania is considerably less in unipolar illness (Bunney Jr. 1978). While L-dihyroxyphenylalanine increases the incidence of hypomania in bipolar patients (Murphy 1982, Prien et al, 1973) catecholamine reuptake blockade or monoamine oxidase inhibition carries a higher risk for the development of mania in these patients (Bunney Jr. 1978).

3.8.2.4 Drugs Depleting the Brain of Catecholamines

3.8.2.4.1 Reserpine and Alpha-Methyl-Dihydroxyphenylalanine

These drugs are associated with a "depletion" of the monoamines dopamine and noradrenaline in the brain. Exposure to reserpine may be associated with depressing effects, which readily occur in vulnerable people (Bunney Jr. 1978). Predicting the effects of reserpine is not easy, but clinically patients on reserpine for hypertension, or as a neuroleptic, have increased depression as a result of the release of the amines stored in the nerve terminals.

Both these drugs may be associated with extrapyramidal syndromes, and may potentiate the effects of haloperidol in the treatment of psychotic patients. A rise of serum prolactin is documented in response to both reserpine and alpha-methyl-dihydroxyphenylalanine.

Clonidine which is an alpha noradrenergic agonist and pindolol which is a beta blocker, are not associated with rises in prolactin (Del Pozo and Lancranjam 1978).

The drugs depleting the central nervous system of noradrenaline, dopamine and 5-hydroxytryptamine are associated with the induction of depression in vulnerable people. Beta

blockade has also been reported to produce depression in some patients, but this requires further study.

3.8.2.4.2 Alpha-Methyl-Para-Tyrosine

Increased incidence of depression may be associated with the use of alpha-methyl-para-tyrosine. This substance has been shown to reduce catecholamine synthesis. Its mode of action is by inhibition of tyrosine hydroxylase, which is the enzyme of the rate limiting step in dopamine synthesis.

There is evidence that alpha-methyl-para-tyrosine is an effective antimanic agent (Brodie et al, 1971). The clinical usefulness of alpha-methyl-para-tyrosine is unfortunately limited by its nephrotoxicity.

3.8.2.5 Lithium

Lithium has multiple effects, including reducing release of noradrenaline, and facilitating the uptake of noradrenaline in synaptosomes. This suggests reduced noradrenaline in the synapse. This is difficult to correlate with the effect on depression. It appears that only the bipolar depressives are potentially responsive to lithium. It also interferes with the development of super-sensitivity of alpha and beta, adrenergic and dopaminergic receptors. There is good evidence for the effect of lithium on the second messenger system (adenylate cyclase system) (Bellmaker 1983). All these effects tend to reduce the functional activity of the catecholamine systems. Support is found here for antimanic action, but does not explain the antidepressant effects in a small number of depressives.

3.8.2.6 Neuroleptics

The evidence that neuroleptics are effective agents in management of mania is legion. Haloperidol is one of the most useful agents in the control of mania, and is a standard drug in the management of this condition. Virtually all

neuroleptics are, however, effective antimanic agents. Chlorpromazine was for a long time the preferred drug in the treatment of mania.

The neurotransmitter profiles for neuroleptics are variable, dopamine, noradrenaline, 5-hydroxytryptamine, histamine and acetycholine may be involved (Ban 1969). All effective antimanic neuroleptics must influence the significant neurotransmitters in mania, the best candidates are noradrenaline and dopamine. An increase in noradrenaline function has generally been favoured as the significant transmitter system in mania; an examination of all neuroleptic profiles in fact favours dopamine (see section on pimozide). The antimanic effects of lithium probably favours noradrenaline. The antimanic dopamine component of neuroleptics is probably mediated by D_2 receptors. A discussion on concentration of dopamine antagonists at therapeutic doses occurs elsewhere.

Pimozide is of great importance due to its rather specific dopamine antagonism (Arden et al, 1970). The blocking by pimozide of noradrenaline receptors seems to be variable depending on the preparations, but only occurs in high concentrations. There is blocking of noradrenaline receptors and of noradrenaline associated adenylate cyclase at these high concentrations (supra-therapeutic).

Extrapyramidal effects are relatively reduced due to pimozide having a fairly high affinity for cholinergic receptors (Yamamura et al, 1976).

Post and co-workers reported in 1980 on the effects of pimozide in mania. A small group of patients were shown to improve on treatment with pimozide, in a similar way to that associated with response to routinely used phenothiazines (Post et al, 1980). This report was later supported by Cookson, Silverstone and Wells (1981).

The efficacy of pimozide in mania increases the support for the view that dopamine is involved in the pathophysiology of mania.

Sulpiride is a drug which has a rather selective dopamine D_2 receptor antagonism. A "pilot" study conducted on fifteen manic patients suggests that sulpiride in high doses is effective in mania (Hart 1982). If this is correct the localisation to a D_2 receptor will be further strengthened. A problem with sulpiride is, however, that it affects other monoamines, i.e. noradrenaline and 5-hydroxytryptamine included.

Claims that sulpiride is an antidepressant in low doses are in line with claims that flupenthixol is also an antidepressant at low doses. The possibility being that sulpiride may have a higher affinity for autoreceptors influencing neurones via this mechanism. A further possibility is that the anticholinergic aspects of neuroleptics may be responsible for the antidepressant activity of these drugs.

3.9 CATECHOLAMINE METABOLITES AND PRIMARY AFFECTIVE DISORDERS

3.9.1 Homovanillic Acid

Homovanillic acid is a metabolite of dopamine by deamination and o-methylation.

The study of homovanillic acid as a means of obtaining indirect information about dopamine appears to have some validity (Moir et al, 1970). There is controversy about the cerebrospinal fluid levels of homovanillic acid in primary affective disorders. The weight of evidence in the depressive phase is in favour of lowered levels of homovanillic acid (Goodwin et al, 1973, Mendels et al, 1973). Elevated levels have been described in severe mania (Post et al, 1973), but not in hypomania. This rise in homovanillic acid has been attributed to the "increased motor activity". The significance of such a statement requires reconsideration. A study comparing bipolar depressives with their manic counterparts showed higher levels of homovanillic acid in manics compared to the depressives (Bowers 1974). Here the accummulation of homovanillic acid was investigated using the probenicid technique.

3.9.2 3-Methoxy-4-Hydroxyphenylglycol

Both urinary and cerebrospinal fluid 3-methoxy-4-hydroxy-phenylglycol have been investigated in mania and depression, Cerebrospinal fluid 3-methoxy-4-hydroxyphenylglycol appears not only to be less reliable than urinary 3-methoxy-4-hydr-oxyphenylglycol, but reported results are so variable that it is difficult to draw conclusion from them. Urinary 3-methoxy-4-hydroxyphenylglycol will, therefore, be reviewed in more detail.

Approximately 50% of the urinary 3-methoxy-4-hydroxyphenyl-glycol is derived from the brain, while the other half probably occurs as a result of peripheral sympathetic act-ivity. Lowered urinary 3-methoxy-4-hydroxyphenylglycol has been reported in depression. On successful treatment these patients showed an increased output of urinary 3-methoxy-4-hydroxyphenylglycol (Maas et al, 1968, Schildkraut et al, 1971). The change in 3-methoxy-4-hydroxyphenylglycol does not appear to be related to the amount of agitation, or retardation in these patients (Maas 1973). Bipolar patients appear to have lower levels than unipolar patients (Schild-kraut et al, 1973). This has been found by other workers as well, for example, Maas.

Tricyclic drugs themselves may have an influence on the lev-els of 3-methoxy-4-hydroxyphenylglycol which may give rise to difficulties in interpretation. The physical state of the patients does not appear to affect the 3-methoxy-4-hyd-roxyphenylglycol levels materially (Bond et al, 1975).

Depressed bipolar patients appear to excrete decreased quan-tities of 3-methoxy-4-hydroxyphenylglycol. Unfortunately not all depressives behave in this fashion. Maas and others reported that schizophrenic syndromes associated with depres-sion also seem to have lowered levels of 3-methoxy-4-hydroxy-phenylglycol (Maas et al, 1969). Those depressives with lowered 3-methoxy-4-hydroxyphenylglycol responded better to imipramine and desmethylimipramine, while those with higher

3-methoxy-4-hydroxyphenylglycol responded less well to these drugs. Possibly those with higher levels of 3-methoxy-4-hydroxyphenylglycol respond better to amitriptyline.

3.10 SELF-STIMULATION

There remains much controversy over the significance of self-stimulation and of the neuronal systems, which support this behaviour.

The concept of a reward system arises due to the fact that behaviour, which is associated with stimulation by electrodes placed in certain brain locations, will be repeated in order to reproduce the stimulation. The behaviour which results in stimulation appears to be reinforced.

The catecholamines have been widely held to be the transmitter systems involved; much controversy, however, still remains.

A system which has much support for sustaining self-stimulation is the noradrenergic system, which arises in the locus coeruleus. The projections run in the dorsal tegmental noradrenergic bundle. It has been claimed that the greatest degree of self-stimulation arises from electrodes placed in areas of highest concentration of catecholaminergic neural elements (German et al, 1974). This is seen in the path of the medial forebrain bundle where overlap of the dorsal noradrenergic bundle, the ventral noradrenergic bundle and the dopaminergic systems (mesolimbic/cortical and nigro-striatal) occur (Ungerstedt 1971). Segal and Bloom presented evidence that stimulation of the locus coeruleus activated the dorsal noradrenergic bundle and was reinforcing (Segal et al, 1974). Destruction of the dorsal noradrenergic bundle by 6-hydroxydopamine abolished the response in the hippocampus. Rewarding effects could occur on activation of the dorsal noradrenergic bundle with ensuing inhibition of hippocampal pyramidal cells.

There is conflicting evidence surrounding these phenomena as it is probable that technical factors here led to the failure by certain groups to obtain self-stimulation from the locus coeruleus. Clarity has not been obtained as certain conflicting data exists (Crow et al, 1972).

Destruction of the dorsal noradrenergic bundle does not abolish the reinforcing effects of locus coeruleus stimulation, nor does damage to the locus coeruleus interfere with reinforcement from dorsal noradrenergic bundle stimulation (Crow RM 1976, Crow TJ 1976). This evidence does not rule out the dorsal noradrenergic bundle and locus coeruleus in reinforcement, but certainly casts doubt on it being the only system involved. Sites which support self-stimulation certainly lie along the path of the dorsal noradrenergic bundle.

Crow reported that self-stimulation behaviour with placement in the locus coeruleus on the one side was associated with increased 3-methoxy-4-hydroxyphenylglycol on the same side in the cortex (Crow TJ 1973). This is cited as support for the coeruleus-cortical noradrenergic system being involved in self-stimulation behaviour. Dopamine has also been shown to have increased release in association with self-stimulation.

There is a suggestion from the evidence that catecholamines are involved in intracranial self-stimulation and that some differences exist in the functions of dopamine and noradrenaline in this phenomenon.

Dopamine appears to be associated with driving of behaviour and noradrenaline seems to be associated with learning and regulation of behaviour (Ursin et al, 1966). Apomorphine leads to poorly integrated increased locomotor activity in normal animals. At high doses sniffing, gnawing etc. occurs - generally ill-regulated locomotor activity. Amphetamines produce heightened locomotor activity which is well integrated. This is probably due to mesolimbic, dopaminergic

involvement (Ungerstedt et al, 1973).

Noradrenergic lesioned animals show little reduction of motor activity, but on operant tasks they learn much more slowly and regulation of behaviour is poorer (Ljunberg et al, 1973). Here the evidence is that the ventral bundle lesion interferes with learning, while the dorsal lesioned animals are not altered, except under the influence of amphetamine when they fail to perform.

3.10.1 Hippocampal Self-Stimulation

Areas of highest concentration of noradrenaline do not seem to support self-stimulation in the hippocampus (Ursin et al, 1966). Stimulation of hippocampal pyramidal cells of C.A.3 area is supporting of self-stimulation and excitatory to pyramidal cells. The inhibition of other pyramidal cells by the dorsal noradrenergic system terminals appears to indicate complex and ill-understood relationships.

3.10.2 Ventral Noradrenergic Bundle

The degree to which self-stimulation is supported by the ventral noradrenergic bundle is unclear, and the extent to which contamination with dopamine elements occurs, remains to be clarified. Studies certainly have been done, which suggest that this system may be involved (Ritter et al, 1975). Evidence that the ventral noradrenergic bundle is involved in learning was presented by Ljunberg and Ungerstedt (1973). Lesions of the ventral noradrenergic bundle interfered with learning. The fact that amphetamines increase locomotor activity and lead to improved regulation of behaviour, while apomorphine produces poorly regulated hyperactivity supports the view that noradrenaline is involved in learning and the regulation of behaviour.

3.10.3 Dopamine Systems and Self-Stimulation

Reports that substantia nigra cells support self-stimulation

remain problematic. The problem being one of overlap with other systems, for example, noradrenergic and medial forebrain bundle elements (Crow TJ 1972). There seems to be difficulty about separating the effects primarily of noradrenaline and those of dopamine. Dopaminergic terminals in the nucleus accumbens have been reported to support self-stimulation (Phillips et al, 1975).

Critical areas which support self-stimulation appear to be areas which have dopamine terminals, for example, entorhinal cortex and cingulate cortex (Collier et al, 1977).

3.10.4 Intracranial Self-Stimulation in Man

Experimental data on intracranial stimulation in man is understandably limited. Reports on stimulation of the septal area, mesencephalic tegmentum, amygdala and caudate nucleus by Heath (1963) constituted the earliest investigations. Stimulation of the tegmental area was associated with elevation of mood, while septal effects had a sexual component in a proportion of electrode placements.

A larger series of patients was reported by Sem-Jacobsen and Torkildsen (1960). The sites of stimulation were widely distributed; ventromedial frontal lobe, parietal lobe, temporal lobe, mesencephalon and hypothalamus. Experiences of "pleasure" could be illicited in many of these areas. The mid-brain tegmentum, posterior and mid-hypothalamus were found to support self-stimulation in man (Bishop et al, 1963).

Limitation to stimulation experiments in man are obvious. Lack of histological confirmation of electrode placement, and less accurate mapping are to be expected. Nevertheless, areas which support self-stimulation seem to relate to the catecholamine systems (Nobin and Bjorklund 1973). Much of the animal experimental work is supported by that carried out in man. Reinforcement and mood elevation, or pleasure, are regular companions of intracranial self-stimulation in man. Here is further evidence that catecholamines are important

in mood and motor regulation.

3.11 EFFECTS OF DRUGS ON INTRACRANIAL SELF-STIMULATION

3.11.1 Psychoactive Agents

The drugs which influence intracranial self-stimulation are those psychoactive agents which influence mood and activity. These drugs are also very important in primary affective disorders. The systems involved seem to be closely related to those systems previously under consideration in the control of motor activity, motivation and the learning of behavioural strategy and possibly mood.

3.11.2 Drugs which Depress Catecholamine Function

Depletion of catecholamines as occurs with reserpine, is associated with reduction of intracranial self-stimulation. Interference with the synthesis of catecholamines as occurs with alpha-methyl-para-tyrosine, attenuates intracranial self-stimulation.

Blockade of catecholamine post-synaptic receptors reduce rates of intracranial self-stimulation. Both phenothiazines and butyrophenones have a profound influence on intracranial self-stimulation. These are potent antimanic agents. Pimozide has also been reported to significantly reduce self-stimulation. Certainly the report that pimozide has a strong influence supports the contention that dopamine is involved in intracranial self-stimulation (Crow TJ 1973). (See section on pimozide in mania).

Phenoxybenzamine, is an alpha-adrenergic blocking agent and has a rather milder effect in reducing intracranial self-stimulation (Zarevics et al, 1977). Inhibition of dopamine beta-hydroxylase does not abolish intracranial self-stimulation.

3.11.3 Drugs which Enhance Catecholamine Function

Blocking of reuptake of catecholamines from the synaptic cleft produces good enhancement in intracranial self-stimulation. Cocaine has a powerful enhancing effect, probably due to catecholamine reuptake blockade. Cocaine produces euphoria in man. The antidepressants also enhance self-stimulation, but the reuptake blockade affects a wider range of neurotransmitters. Randrup and Braestrup (1977) emphasize the dopamine reuptake blocking of antidepressants. This appears to be significant with nomifensine, while many other antidepressants have a considerable action on noradrenaline, and to a greater or lesser extent, 5-hydroxytryptamine. Imipramine certainly has a predominant effect on noradrenaline and enhances intracranial self-stimulation significantly.

3.11.3.1 Monoamine Oxidase Inhibitors

The monoamine oxidase inhibitors are associated with decreased breakdown of catecholamines by inhibition of the enzyme monoamine oxidase. Intracranial self-stimulation is enhanced by this group of drugs which increase catecholaminergic function.

3.11.3.2 Amphetamines

Amphetamine has a positive effect on intracranial self-stimulation. The modes of action are at least three-fold:-

a) increased release of catecholamine and so increase availability of catecholamine at the postsynaptic receptors;

b) a weak monoamine inhibiting action;

c) some blocking effect on reuptake of catecholamines from the synaptic cleft.

Amphetamines produce an increase in intracranial self-stim-

ulation whether the electrode placement is in the nucleus accumbens or in the corpus striatum (Stephens and Herberg, 1977).

3.11.3.3 Dopamine Agonists

Apomorphine generally increases intracranial self-stimulation except for a few placements of the electrodes. The dopaminergic system is problematic due to the existence of inhibitory receptors.

3.11.3.4 Bicyclic Agents

Bicyclic compounds which are noradrenergic reuptake inhibitors are associated with facilitation of intracranial self-stimulation, but those drugs associated with 5-hydroxytryptamine function enhancement are associated with attentuation of intracranial self-stimulation (Sulser 1971).

3.11.4 The Neuronal Substrate of Intracranial Self-Stimulation

Crow TJ (1973) believes that two systems are involved with intracranial self-stimulation:-

a) the dopaminergic system with cell bodies in Areas A.9 and A.10, and

b) the noradrenergic system with cells lying in the locus coeruleus. Stimulation of this system has been shown to increase the noradrenaline turnover in the ipsilateral cortex (Anlezark et al, 1973).

3.12 ENDOCRINE SYSTEM

3.12.1 Abnormalities of Cortisol Secretion

Increased secretion of cortisol in depressed patients is well established (Carroll 1972, Carroll et al, 1979). The secretion may be particularly increased in the afternoon and night,

thus producing a flattened diurnal curve, by comparison with that occurring in the normal state (Carroll et al, 1979). This abnormal secretion occurs in about 50% of depressives and is not a non-specific stress phenomenon. Recovery is associated with a return to normal (Stokes et al, 1975). Apart from the hypersecretion of cortisol and adrenocorticotropic hormone there is a resistance to suppression with dexamethasone (Browne et al, 1979). This occurs in slightly less than 50% of patients who are biologically depressed, or by Klein's classification "endogenomorphic depressives" (Klein 1974).

The regulation of cortisol secretion via the hypothalamus appears to be controlled by excitatory and inhibiting factors. Cholinergic and serotonergic activity (Scapagnini et al, 1971) have stimulating effects, while noradrenaline (Scapagnini et al, 1972) and gabergic functions have inhibitory effects on corticotropic hormone releasing factor. Defective noradrenergic mechanisms may be involved in depressives, resulting in reduced inhibition of corticotropic hormone releasing factor, hence increased levels of adrenocorticotropic hormone and cortisol. Cortisol abnormalities are now well documented in depressive illness, and are considered here as evidence for possible catecholamine dysregulation in primary affective disorder. It also constitutes a prototype of neuroendocrine testing as a possible means of looking at neuronal functional integrity in psychiatric disorders.

3.13 ELECTROCONVULSIVE THERAPY

Electroconvulsive therapy is recognised by many authorities as the most effective treatment of major depressive illness. Numerous studies bear witness to this including that of West (1981).

The mode of action of electroconvulsive therapy is of importance in this context. Kety et al, (1969) demonstrated an increased synthesis and utilization of noradrenaline in the rat brain after electroconvulsive shock; this was shown in the

catecholamine rich areas. The activity of tyrosine hydroxylase was increased (Musacchio et al, 1969) under the influence of electroconvulsive shock. Beta adrenergic receptors become less sensitive with multiple electroconvulsive shocks (Pandey et al, 1979).

Dopamine has also been shown to be affected by electroconvulsive therapy, both increases in brain dopamine (Cooper et al, 1968) and in the response of dopamine receptors (Green et al, 1977) have been demonstrated. Cerebrospinal fluid and brain levels of homovanillic acid were increased by multiple electroconvulsive treatments (Cooper et al, 1968).

Here is further evidence of the possible involvement of both dopamine and noradrenaline in the therapeutic effects of electroconvulsive treatment, hence in primary affective disorders.

3.14 DIFFERENTIAL EFFECTS OF ANTIMANIC AGENTS ON MOTOR ACTIVITY AND MOOD IN MANIA

Evidence of the relative effects of various antimanic agents on dopamine and noradrenaline can be correlated with effects on motor activity, and elevation of mood respectively. Reserpine acts in a similar fashion on dopamine and noradrenaline, depletion occurring in both amine stores. Reserpine influences the course of motor activity and elevated mood in mania by a parallel reduction in both.

Alpha-methyl-para-tyrosine behaves in a similar manner to reserpine with a parallel and equal reduction of motor activity and mood. Alpha-methyl-para-tyrosine "depleted" the neuronal stores of both dopamine and noradrenaline, without preference (Brodie et al, 1971).

A number of types of neuroleptics, phenothiazines, butyrophenones and diphenylbutylpiperidine have been studied in detail for the manner in which they reverse the manic state. The evidence points to a more substantial influence on motor

activity than on mood. These drugs are more potent dopamine than noradrenaline blocking agents (Goodwin 1979). Pimozide, in fact, at therapeutic doses, has virtually no action on noradrenaline, thus it is relatively selective for dopamine (Anden et al, 1979).

Lithium appears to have a more favourable effect on the affective component of mania (Goodwin 1979). The effects of lithium on the catecholamines are discussed. It is difficult to be sure that noradrenergic effects are greater than dopaminergic effects, but certainly interference with adenylate cyclase seems to favour noradrenaline. Certain of the other effects also favour noradrenaline. It is, therefore, possible that the change in mood may correlate with a predominance of noradrenergic influences rather than of dopamine.

Dopamine-beta-hydroxylase inhibitors may also produce more profound influence on mood than on motor activity in mania (Goodwin 1974). Psychotic symptoms appear to worsen with fusaric acid. This upholds the contention that mood may be noradrenaline regulated and motor activity (and psychotic disorganisation) dopamine regulated. Dopamine-beta-hydroxylase inhibition requires further evaluation.

3.15 SUMMARY OF EFFECTS OF PSYCHOACTIVE AGENTS IN PRIMARY AFFECTIVE DISORDERS

a) Those substances which enhance catecholamine function in the central nervous system improve depression and increase the risk of mania in bipolar patients.

b) Those substances which mute central catecholamine function are associated with increased risk of depression, or an attentuation of mania.

c) Most of the evidence supports this view, despite some discrepancies which have been reported, for instance L-dihydroxyphenylalanine producing depression. The

evidence supporting the view for catecholamine function being fundamental to the pathophysiology of primary affective disorders, is greater than for any other single pathophysiological or psychopathological view. It is probable that dopamine plays as important a role in primary affective disorder as does noradrenaline, and that their individual dysfunction and interaction is part of a complex transmitter system disturbance.

3.16 PROLACTIN

It has been known since 1938 that prolactin is a lactogenic substance having been found in cow pituitary. The chemistry of prolactin is very similar to that of growth hormone, these hormones probably having a common origin. In 1970 evidence was published that prolactin was separate from growth hormone in human blood (Frantz and Keinberg, 1970). The two hormones can be easily separated by radioimmunoassay.

Prolactin affects behaviour in more primitive vertebrates such as birds, in particular reproductive behaviour. There are two phases the first being sexual, and the second being the "parenting" or maternal phase. The second phase is profoundly influenced by prolactin. In man very little is known about its behavioural effects, although its influence on lactation in "mothering" is well established. There is also evidence that prolactin is a stress hormone, being sensitive to both physical and psychological stress (Kelly et al, 1974). This does, of course, make the investigation of prolactin more difficult and the results more tentative (Sachar 1965). The study of prolactin may, however, give information about abnormal events in the nervous system (Horrobin 1974); not so much because it may be causally related to the psychiatric condition, but rather in that it may reflect pathology within the nervous system. It is of interest that prolactin may stimulate activity of dopaminergic neurones in the limbic and striatal systems, and that it may interact with the effects of neuroleptics on dopa-

mine systems (Perkins and Westfall, 1978). There may also be some effect on acetylcholine. These systems may all be extremely important in primary affective disorders.

3.16.1 Regulation of Prolactin

While the regulation of prolactin is complex there are a few dominant regulatory factors. These may vary with the state of the person (e.g. post-partum).

3.16.1.1 Negative Control

Prolactin is able to regulate its own secretion by a short negative feed-back loop, influencing the tubero-infundibular dopamine neurones.

3.16.1.2 Tonic Inhibitory Control

An unusual mode of regulation is by tonic inhibition of prolactin secretion under the control of the hypothalamus. Activity of the tubero-infundibular dopaminergic tract decreases the secretion of prolactin by the dopaminergic prolactin inhibiting factor. (See section on tubero-hypophyseal system and its relation to the portal system.) (Jimenez et al, 1978).

3.16.1.3 Suckling

Stimulation of the breast and nipple especially post-partum, have a profound stimulating effect via the hypothalamus on the secretion of prolactin.

3.16.1.4 Serotonergic Regulation

Serotonergic neurones regulate the release via the prolactin releasing factor.

3.16.1.5 Stress

Stress may increase prolactin levels but what the function of this may be is not understood. The reduction of fertility under stress may be mediated via this mechanism (Smith 1979).

3.16.1.6 Physiological Factors

Sleep, exercise, oestrogens and pregnancy may all increase prolactin levels.

3.16.1.7 Pathological Factors

A variety of pathological factors may give rise to an increase in prolactin, for instance, hypoglycemia, liver failure, adenomata, etc.

3.16.1.8 Pharmacological Factors

Antipsychotic agents which are dopamine antagonists raise prolactin levels. Chlorpromazine has been used as a challenge for the prolactin system in this study (Kolakowska et al, 1981.

Reserpine, methyl-dopa, oral contraceptives and thyrotropin releasing hormone have all been associated with a rise of prolactin levels in the serum. The reverse effects are well recorded with apomorphine, L-dihydroxyphenylalanine and bromocriptine (Aidara et al, 1981).

3.16.1.9 Antidepressants

No consistent effects on prolactin occur with different antidepressants. Amitriptyline and imipramine have no effect. Dibenzepin produces a marked increase in prolactin by an unknown mechanism. Antidepressant drugs with predominant serotonergic effects tend to produce a rise in prolactin. Zimelidine does not, however, do so. Monoamine

oxidase inhibitors tend to increase levels of prolactin. Some inhibition of dopaminergic mechanisms by serotonergic systems may occur. Nomifensine decreases levels of prolactin. 5-Hydroxytryptamine may produce an increase in prolactin levels. (Meltzer et al, 1978, Meltzer et al, 1979).

3.16.1.10 Electroconvulsive Therapy

Electroconvulsive therapy has been reported to be associated with a transitory rise of prolactin. This is presumably due either to the enhancement claimed to occur in dopaminergic systems, or to the non-specific stress with electroconvulsive treatment.

3.17 SUBSTANCES ALTERING DEPRESSION AND PROLACTIN LEVELS

Reserpine and alpha-methyl-dopa have been well documented as being responsible for induction of depression (McKinney and Kane 1967). These drugs are associated with depletion of central dopamine and elevation of serum prolactin levels.

The possibility that neuroleptics (dopamine antagonists) may be associated with the production or promotion of depression has clinical, and some documented, support (McGlashan and Carpenter 1976).

There is a suggestion that high doses of certain antidepressants, such as nortriptyline, may be associated with a reversal of the normal therapeutic effect (Hollister 1978). The effect of antidepressants on prolactin is very variable, and may be dependent on dosage, amine profile of the antidepressant, and certain unknown factors. Increased serotonergic activity, due to the effects of serotonergic antidepressants may be associated with an increase in prolactin levels. Dibenzepin has also been reported to produce lactorrhoea; the mechanism here is not understood. Nomifensine may reduce prolactin levels by its dopaminergic activity. Antidepressants are variable in their effects, but do not generally affect prolactin. They are, of course, able to

improve the clinical picture of depression.

3.18 ELECTROCONVULSIVE THERAPY AND PROLACTIN IN DEPRESSION

It has been suggested from animal experiments that electroconvulsive therapy may increase the sensitivity of the postsynaptic monamine receptors of dopamine, noradrenaline and 5-hydroxytryptamine in the brain (Modigh 1975, Evans and Modigh 1977). Modigh, Evans and Modigh produced evidence to support the receptor sensitivity concept of electroconvulsive therapy. Of particular importance is the time frame, their effects resulted from one electroconvulsive therapy treatment per twenty four hours and not from hourly treatment. This reproduces the maximal efficacy of electroconvulsive therapy when used in treating depressed patients (Ohman et al, 1976).

Christie and associates studying depressives were unable to show any change in prolactin levels in response to 0,75mg. of apomorphine given subcutaneously before, and after, treatment with electroconvulsive therapy (Christie et al, 1982).

The Skrabanek study looked at the acute effects of electroconvulsive therapy on prolactin levels, and were able to show an increase in prolactin 5-24 minutes after treatment with electroconvulsive therapy. This looks very much like a stress effect (Skrabanek et al, 1981).

Coppen and associates measured prolactin response to thyrotropin releasing hormone in depressed patients. These workers were unable to find evidence of significant disturbance of 5-hydroxytryptamine effects on prolactin. Following electroconvulsive therapy the patients showed an increased prolactin sensitivity of central 5-hydroxytryptamine receptors (Coppen et al, 1980).

3.19 PROLACTIN IN DEPRESSION

Horrobin et al, (1976) reported increased levels of prolactin in depression, as had Sachar et al, in 1973. The problem of non-specific stress effects constitutes a difficult problem to solve. If depressive illness is a complex amine system interactional disorder it is possible that a sub-group of depressives may show an elevation of prolactin while others may be normal, or even low. This will be discussed more fully later in considering dopamine and motor function in depressive illness. Carroll reported an increased secretion of prolactin in major depressives during the night, this being abnormally high and not part of the normal diurnal variation of prolactin secretion. He observed that daytime levels of prolactin were relatively normal in depressed patients (Halbreich et al, 1979).

Meltzer and associates found no abnormalities of prolactin production in depressives. A conflicting report by Winokur et al, in 1982 found that prolactin response to thyrotropin releasing hormone showed a much greater variability, with both increased and decreased levels being evident. This may relate to previous comments on the complex nature of the depressive syndrome (Meltzer et al, 1978).

A study of depressives by Brambilla and associates indicated a rise of the prolactin response to a thyrotropin releasing hormone challenge (Brambilla et al, 1981).

Bunney and co-workers reported on effects of beta-2 adrenergic stimulation on prolactin levels in depressives. They found no change at all. Beta-2 adrenergic receptors do not seem to be involved in the control of prolactin secretion (Bunney et al, 1981).

Judd and associates using a methadone hydrochloride challenge found a blunted response of prolactin in depressed patients and commented that the basal levels were also low! (Judd et al, 1982)

Frazer (1975) and Caspar (1977) failed to show an impairment of growth hormone response to apomorpine in depressed patients.

3.20 PEPTIDES AND AFFECTIVE DISORDERS

A large number of peptides have been found in the brain and presumably many play a role in behaviour. The role of peptides in psychiatric disorders is even more obscure. The response of thyroid stimulating hormone to thyrotropin releasing hormone has been shown to be blunted in a proportion of patients with biological depression (Kirkegaard et al, 1978). This is now a standard test in affective disorder units.

The role of endorphins in affective disorders is unclear. Endorphins have certainly been shown to produce behavioural effects similar to the opiates (Koob 1984). Opiate-like activation is produced when beta-endorphine is injected intra-ventricularly. This action may be related to mesolimbic dopamine transmission. Endorphins are generally inhibitory to dopamine inhibition. The role of endorphins and other peptides in mood and motor regulation requires further investigation.

3.21 PATHOPHYSIOLOGY IN SCHIZOPHRENIA

Schizophrenia is possibly a hyperdopaminergic state. Crow has classified schizophrenia into type I and type II, drawing some distinction between the acute active schizophrenics and the insidious deteriorating schizophrenias. The active psychotic state, whether schizophrenic or manic, respond better to neuroleptics than do the so called "negative symptom" schizophrenias of type II, according to Crow (1980). Antipsychotic effects of neuroleptics have been well related to their dopamine antagonism (Matthysse 1973). Dopamine antagonism by neuroleptics can be monitored by the measurement of prolactin. This has been one of the most extensively studied aspects of prolactin in psychotic disorders (Gruen

1978). Prolactin increment as a prediction of response of psychotic states to dopamine antagonists is controversial. Studies of prolactin in schizophrenia do not support a hyper-function of the dopamine regulating system of prolactin. It does not seem to reflect the abnormality (should it exist) in other dopamine systems in schizophrenia (Gruen et al, 1978, Kolakowska 1979).

CHAPTER 4

PROCEDURES

4.1 INTRODUCTION

The difficulty of measuring subtle intracranial events is self-evident and still remains our greatest challenge. The present study was conceived in an attempt to investigate subtle brain function in primary affective disorders. The probabilities are high that neurobiophysiological disturbances underlie the manifestations of primary affective disorders; this is strongly supported by previous research as indicated in Chapter 3.

Much evidence has been reviewed which suggests involvement of the catecholamines and, in particular dopamine, in primary affective disorders. The literature review draws attention to evidence suggesting the possible involvement of dopamine in motor behaviour as well as in primary affective disorder. Disturbance of motor behaviour is fundamental to primary affective disorders, in particular the bipolar variety! It is unlikely that the pathology in primary affective disorders will be found in one system only, but rather a complex interactional disturbance involving a number of systems is likely to underlie the entire clinical picture.

The emphasis in this study is on dopamine in primary affective disorders. A fundamental assumption in the formulation is that the functional state of a dopaminergic system, which can be indirectly monitored may reflect the disturbance of less accessible dopamine systems. This possibility can be assumed as a result of the commonality which exists in dopamine systems. Abnormalities of transmitter function are probably more likely to be reflected throughout the dopamine systems of the brain than dysfunction of dopamine receptors. The heterogeneity of dopamine receptors has been considered previously, for instance, adenylate cyclase dependent and

adenylate cyclase nondependent receptors. This heterogeneity decreases the probability that functional disturbance of the one type of dopamine receptor will necessarily be reflected in another type of dopamine receptor.

An attempt is being made to find a change in dopamine function in primary affective disorders by comparing dopamine function in well-phase with that of illness-phase. While it is thought that the mesolimbic and nigrostriatal systems are more intimately involved with motor function, "measurement" of these systems remains problematic. The indirectly accessible tuberohypophyseal dopamine system was chosen for investigation. It is hoped that this system may demonstrate changes in primary affective disorders that reflect similar dysfunction in the motor dopamine system.

4.2 THE EXPERIMENTAL SYSTEM

Dopamine profoundly regulates prolactin as has been stated previously (Jimenex et al, 1978). Investigation of the dopamine/prolactin axis has a real possibility of reflecting the state of other intracranial dopamine systems. The dopamine receptors involved in prolactin regulation have been reviewed; dopamine exerting an inhibitory influence on prolactin secretion. Dopaminergic systems may be abnormal in primary affective disorders (Post et al, 1980). Dopamine receptors regulating prolactin have much in common with D_2 receptors and are probably variants of D_2 receptors. This means that there is a fairly strong similarity between the test system and putative motor drive system. The choice of a challenge technique for the investigation of the dopamine prolactin axis was influenced by the fact that the prolactin system is very responsive to stress. It was thought, therefore, that a challenge would possibly produce more reliable results. A further factor was that a challenge would probably put the system under stress and therefore may demonstrate deviations not seen in an unstressed situation. Rapid fluctuations of prolactin which may occur at rest reduce the reliability of these readings. It is postulated

that the "stressed" system is more likely to produce a consistent pattern of response.

The pharmacological challenge was conducted in two parts, the one being when the patient was ill, and the other when the patient was well or significantly improved.

Two agents were used in the actual challenge investigation which was conducted on two separate days. The first agent being L-dihydroxyphenylalanine which was given orally in a single dose of 500mg. on the first day. L-dihydroxyphenylalanine enhances dopaminergic activity and is associated with an increased inhibition of prolactin secretion. The second agent to which the patient was exposed was chlorpromazine, a dose of 25mg. by intramuscular injection being given. This drug blocks dopamine thereby reducing the tonic dopaminergic inhibition on prolactin with a resultant increased secretion. Details of the procedure are recorded later, but of primary importance is the fact that this procedure was conducted when the patient was ill and when the patient was recovered or significantly improved.

4.3. SUBJECTS

4.3.1 Selection

The subjects for this study were drawn from admission to the Biological Unit at Tara - The H. Moross Centre. Patients with physical disease or pregnancy were excluded. No patients under the age of sixteen years were included. Informed consent was a prerequisite.

A full psychiatric investigation and evaluation was conducted including the patients' history and mental state examination.

Further information was obtained regarding the patients' social/occupational milieu, previous psychiatric records, psychological testing and observation.

A diagnostic formulation for inclusion/exclusion was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM III) of the American Psychiatric Association. The diagnostic criteria were those appropriate for primary affective disorders.

4.3.2 Diagnostic Criteria

The following are the diagnostic criteria for primary affective disorders according to the DSM III:-

"Diagnostic criteria for major depressive episode

A. Dysphoric mood or loss of interest or pleasure in all or almost all usual activities and pastimes. The dysphoric mood is characterized by symptoms such as the following: depressed, sad, blue, hopeless, low, down in the dumps, irritable. The mood disturbance must be prominent and relatively persistent, but not necessarily the most dominant symptom, and does not include momentary shifts from one dysphoric mood to another dysphoric mood, e.g., anxiety to depression to anger, such as are seen in states of acute psychotic turmoil. (For children under six, dysphoric mood may have to be inferred from a persistently sad facial expression).

B. At least four of the following symptoms have each been present nearly every day for a period of at least two weeks (in children under six, at least three of the first four).

(1) poor appetite or significant weight loss (when not dieting) or increased appetite or significant weight gain (in children under six, consider failure to make expected weight gain)

(2) insomnia or hypersomnia

(3) psychomotor agitation or retardation (but not merely subjective feelings of restlessness or being slowed down) (in children under six, hypoactivity)

(4) loss of interest or pleasure in usual activities or decrease in sexual drive not limited to a period when delusional or hallucinating (in children under six, signs of apathy)

(5) loss of energy; fatigue

(6) feelings of worthlessness, self-reproach, or excessive or inappropriate guilt (either may be delusional)

(7) complaints of evidence of diminished ability to think or concentrate, such as slowed thinking, or indecisiveness not associated with marked loosening of associations or incoherence

(8) recurrent thoughts of death, suicidal ideation, wishes to be dead, or suicide attempt

C. Neither of the following dominate the clinical picture when affective syndrome (i.e., criteria A and B above) is not present, that is, before it developed or after it was remitted:
(1) preoccupation with a mood-congruent delusion or hallucination (see definition below)
(2) bizarre behaviour

D. Not superimposed on either Schizophrenia, Schizophreniform Disorder, or a Paranoid Disorder.

E. Not due to any Organic Mental Disorder or Uncomplicated Bereavement.

Fifth-digitcode numbers and criteria for subclassification of major depressive episode

(When psychotic features and Melancholia are present the coding system requires that the clinician record the single most clinically significant characteristic.)

(b) the depression is regularly worse in the morning
(c) early morning awakening (at least two hours before usual time of awakening)
(d) marked psychomotor retardation or agitation
(e) significant anorexia or weight loss
(f) excessive or inappropriate guilt

2- Without Melancholia

0- Unspecified

Diagnostic criteria for a manic episode

A. One or more distinct periods with a predominantly elevated, expansive, or irritable mood. The elevated or irritable mood must be a prominent part of the illness and relatively persistent, although it may alternate or intermingle with depressive mood.

B. Duration of at least one week (or any duration if hospitalization is necessary), during which, for most of the time, at least three of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:
(1) increase in activity (either socially, at work, or sexually) or physical restlessness
(2) more talkative than usual or pressure to keep talking
(3) flight of ideas or subjective experience that thoughts are racing
(4) inflated self-esteem (grandiosity, which may be delusional)
(5) decreased need for sleep
(6) distractability, i.e., attention is too easily drawn to unimportant or irrelevant external stimuli
(7) excessive involvement in activities that have a high potential for painful consequences which is not recognized, e.g., buying sprees, sexual indiscretions, foolish business investments, reckless driving

C. Neither of the following dominate the clinical picture when an affective syndrome (i.e., criteria A and B above) is not present, that is, before it developed or after it has remitted:

(1) preoccupation with a mood-congruent delusion or hallucination (see definition below)

(2) bizarre behaviour

D. Not superimposed on either Schizophrenia, Schizophreniform Disorder, or a Paranoid Disorder.

E. Not due to any Organic Mental Disorder, such as Substance Intoxication.
(Note: A hypomanic episode is a pathological disturbance similar to, but not as severe as, a manic episode.

Fifth-digit code numbers and criteria for subclassification of manic episode

6- In Remission. This fifth-digit category should be used when in the past the individual met the full criteria for a manic episode but now is essentially free of manic symptoms or has some signs of the disorder but does not meet the full criteria. The differentiation of this diagnosis from no mental disorder requires consideration of the period of time since the last episode, the number of previous episodes, and the need for continued evaluation of prophylactic treatment.

4- With Psychotic Features. This fifth-digit category should be used when there apparently is gross impairment in reality testing, as when there are delusions or hallucinations or grossly bizarre behavior. When possible, specify whether the psychotic features are mood-congruent. (The non-ICD-9-CM fifth-digit 7 may be used instead to indicate that the psychotic

features are mood-congruent; otherwise, mood-congruence may be assumed.)

Mood-congruent Psychotic Features: Delusions or hallucinations whose content is entirely consistent with the themes of inflated worth, power, knowledge, identity, or special relationship to a deity or famous person; flight of ideas without apparent awareness by the individual that the speech is not understandable.

Mood-incongruent Psychotic Features: Either (a) or (b):

(a) Delusions or hallucinations whose content does not involve themes of either inflated worth, power, knowledge, identity, or special relationship to a deity or famous person. Included are such symptoms as persecutory delusions, thought insertion, and delusions of being controlled, whose content has no apparent relationship to any of the themes noted above.

(b) Any of the following catatonic symptoms: stupor, mutism, negativism, posturing.

2- Without Psychotic Features. Meets the criteria for manic episode, but no psychotic features are present.

0- Unspecified.

Diagnostic criteria for Bipolar Disorder, Mixed
Use fifth-digit coding for manic episode.

A. Current (or most recent) episode involves the full symptomatic picture of both manic and major depressive episodes intermixed or rapidly alternating every few days.

B. Depressive symptoms are prominent and last at least a full day.

Diagnostic criteria for Bipolar Disorder, Manic

Currently (or most recently) in a manic episode. (If there has been a previous manic episode, the current episode need not meet the full criteria for a manic episode).

Diagnostic criteria for Bipolar Disorder, Depressed

A. Has had one or more manic episodes.

B. Currently (or most recently) in a major depressive episode. (If there has been a previous major depressive episode, the current episode of depression need not meet the full criteria for a major depressive episode.)

Diagnostic criteria for Major Depression

A. One or more major depressive episodes.

B. Has never had a manic episode or hypomanic episode."

4.4. METHODS

4.4.1 Experimental Procedures

Once the subjects had been accepted into the study having duly considered the exclusion and inclusion criteria, they were subjected to a standardised programme.

4.4.2 Wash-Out Period

All patients who, prior to admission, had been on psychotropic agents were withdrawn from these drugs. Those patients who were very agitated or sleepless were allowed limited doses of oxazepam, particularly at night. A 7-10 day wash-out period was observed. This was common practice within the unit under normal circumstances. Those subjects who had not been on psychoactive agents prior to admission were permitted virtually direct admission to the study, once the evaluative process had been completed and inclusion accepted.

4.4.3 Rating

A rating of the subject's mental state was carried out prior to the first pharmacological challenge. The rating scales used were the Hamilton Depressive Rating in the majority of patients and the Pettersen Scale of Mania was used in the presence of hypomania and mania. The rating was repeated prior to the second pharmacological challenge. Thus two lots of rating values were obtained, those when the subject was ill, "illness score" and those when the subject was well, or significantly recovered, "well score".

4.4.4 Treatment

Depressed subjects were treated by conventional means, the majority having received electroconvulsive therapy, while a small proportion were given antidepressants. The standard antidepressant used was maprotiline, although one subject was treated with nomifensine due to her poor tolerance of maprotiline. Manic patients were treated with haloperidol. The second pharmacological challenge was conducted a minimum of two weeks after the withdrawal of haloperidol.

4.4.5 The Challenge Procedure

The technique for both "ill" and "well" challenges was identical. The investigation was conducted under fasting conditions, no food having been taken from 22h00 on the previous day. All procedures were carried out in the morning between 08h00 and 09h00.

4.4.5.1 L-dihydroxyphenylalanine Challenge (Day 1)

The subject was exposed to L-dihydroxyphenylalanine on Day 1. An intravenous line was set up and the base-line blood was taken following which 500mgs. of L-dihydroxyphenylalanine was administered orally. Four subsequent blood samples were taken at 20, 40, 60, 90 minutes after the administration of

L-dihydroxyphenylalanine.

4.4.5.2 Chlorpromazine Challenge (Day 2)

24 - 72 hours after the L-dihydroxyphenylalanine challenge the subjects were exposed to chlorpromazine 25mgs. intramuscularly. This chlorpromazine technique was similar to that of the L-dihydroxyphenylalanine challenge, the blood samples being a baseline sample and five subsequent samples at 20, 40, 60, 90, 120 minute intervals from the time of administration of the chlorpromazine.

All the blood was immediately centrifuged and the serum separated and frozen at -20C, under which conditions it was stored until assay for prolactin was carried out in batches. All samples were appropriately labelled and dated.

The pharmacological challenges were repeated upon significant improvement. Two sets of prolactin readings for each of the L-dihydroxyphenylalanine and chlorpromazine challenges were obtained giving a set of readings for "illness" phase and a set for "well" phase.

4.4.6 The Final Data

The final data containing the relevant variables was therefore constituted in the following way:-

4.4.6.1 "Illness" Phase Data

This data was made up of a set of ratings (Hamilton/Pettersen) and a set of prolactin values in response to the L-dihydroxyphenylalanine and chlorpromazine challenges.

4.4.6.2 "Well"Phase Data

The "well"phase data also consisted of a set of ratings

(Hamilton/Pettersen) and a set of prolactin values in response to the L-dihydroxyphenylalanine and chlorpromazine challenges, these measures having been conducted after significant improvement had occurred.

Two subjects were studied in a depressed (illness) phase and also in manic (illness) phase, as well as recovered (well) phase.

4.4.6.3 Other Variables

A number of other variables were considered in the statistical analysis, these included:-

Age
Sex
Polarity
Mode of Treatment
Weight

Examples of the rating scales and prolactin values can be seen in the raw data.

4.5 PROLACTIN ASSAY BY RADIOIMMUNOASSAY KIT (RIANEN ASSAY SYSTEM)

A radioimmunoassay technique was used to measure the levels of plasma prolactin. The principle of the assay is based upon competition between radioactive labelled antigen and non-labelled antigen (prolactin) for a fixed number of specific antibody binding sites.

A constant and limiting amount of antibody is used and allowed to react with a constant amount of labelled antigen and with samples or standards (unlabelled antigen). The amount of labelled antigen re-acting with the antibody decreases as the quantity of unlabelled antigen, sample or standard, is

increased. If the antibody antigen complex is separated from the unbound tracer the bound radioactive label complex can be counted. Standards may be used to construct a curve from which the values of samples can be obtained.

Separation of the bound from the free antigen is achieved by precipitation of the antigen-antibody complex by the addition of a second antibody which has been developed from the gamma globulin of the primary antibody, in a different species of animal. Precipitation is followed by incubation and centrifugation, and supernatant being discarded.

4.5.1 Primary Antibody

The prolactin antibody (developed in rabbit) is supplied in a vial and stored at 4°C.

4.5.2 Labelled Antigen

A vial of prolactin with radioactive tracer is supplied with the kit and has to be accurately reconstituted with distilled water and stored at 4°C. Precautions in handling this material must be observed and it is not to be used for any in vivo study. Observation of all restrictions were observed as pertinent to this particular material.

4.5.3 Prolactin Standards

Standards of prolactin are supplied with the kit and have to be accurately reconstituted with distilled water. Seven standards are provided ranging from 0, 5, 10, 20, 100 to 200ng/ml. This is standard human prolactin in buffer. Storage at 4°C.

4.5.4 Blank Antiserum

Vials of normal rabbit antiserum forms part of the kit. Storage observed at 4°C.

4.5.5 Control Serum

Human serum with a prolactin concentration of 25ng/ml is supplied. This must be reconstituted as indicated with exactly 1 ml of distilled water and stored at 4°C.

4.5.6 Second Antibody

The second antibody is supplied ready for use and stored at 4°C. It is developed against rabbit gamma globulin (primary antibody).

CHAPTER 5

RESULTS

5.1 RAW DATA

The raw data on twenty seven cases is presented. This data comprises of two groups of subjects, those who were investigated and rated in the depressive phase, and the second group which was investigated and rated in the manic phase. Both groups were re-rated and investigated upon recovery. Standard rating scales were used for scoring, the Hamilton Depressive Scale for the depressive phase and the Pettersen Scale for the manic phase. The actual raw data is included for all twenty seven patients. Twenty one subjects were rated on the Hamilton Scale and eight subjects were rated on the Pettersen Scale giving an effective total of twenty nine sets of raw data. Two subjects were investigated both when manic and depressed. The investigations performed were those previously discussed being pharmacological challenges with L-dihydroxyphenylalanine and chlorpromazine; blood sampling for prolactin was carried out at times 0 (baseline) 20, 40, 60, 90 minutes and an additional sample at 120 minutes for the chlorpromazine challenge. These times are represented in Tables LXXXIX - XLII by the symbols B, C, D, E, F and G respectively.

The raw data presented are the actual values of prolactin for baseline levels and levels at the times indicated in the data sheets, before and after treatment (i.e. "ill" values and "well" values). The discrepancy between the twenty seven subjects and the twenty nine sets of raw data is due to the two subjects who were investigated both when depressed and when manic. The two sets of data for each of these two subjects were dealt with as four separate subjects. The reasons for this are that the number of patients investigated (two) in both phases of bipolar illness is too small to produce significant results, and limitation of the rating instruments do not allow ease of comparison of data through from

depressed to manic phase. Some further comments on these two patients will, however, be made at a later stage.

PATIENT IDENTIFICATION: 1 SEX: F AGE: 68

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ANTIDEPRESSANTS

TABLE I

HAMILTON RATING SCALE FOR DEPRESSION

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. DEPRESSED MOOD	0 - 4	3	0
2. FEELING OF GUILT	0 - 4	2	0
3. SUICIDE	0 - 4	1	0
4. INSOMNIA - EARLY	0 - 2	0	1
5. INSOMNIA - MIDDLE	0 - 2	0	0
6. INSOMNIA - LATE	0 - 2	2	1
7. WORK AND ACTIVITIES	0 - 4	2	0
8. RETARDATION	0 - 4	3	0
9. AGITATION	0 - 2	1	0
10. ANXIETY PSYCHIC	0 - 4	3	1
11. ANXIETY - SOMATIC	0 - 4	1	0
12. ANXIETY SYMPTOMS (G.I.T.)	0 - 2	0	0
13. SOMATIC SYMPTOMS (GEN)	0 - 2	0	0
14. GENITAL SYMPTOMS	0 - 2	0	0
15. HYPOCHONDRIASES	0 - 4	0	0
16. LOSS OF WEIGHT	0 - 2	2	1
17. INSIGHT	0 - 2	0	0
18. DIURNAL VARIATION	0 - 2	0	0
19. DEPERSONALISATION	0 - 4	1	0
20. PARANOID SYMPTOMS	0 - 4	0	0
21. OBSESSIONAL SYMPTOMS	0 - 2	1	1
22. HELPLESSNESS	0 - 4	2	0
23. HOPELESSNESS	0 - 4	3	1
24. WORTHLESSNESS	0 - 4	3	0

PATIENT IDENTIFICATION: 1 SEX: F AGE: 68

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ANTIDEPRESSANTS

TABLE II

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	0.3	4.7
20	0	1.6
40	0	2.1
60	0	4.2
90	0	2.0

TABLE III

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	0	3.6
20	4.6	2.1
40	6.1	6.6
60	15.5	13.3
90	8.7	13.4
120		14.7

PATIENT IDENTIFICATION: 3 SEX: F AGE: 59

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ELECTROCONVULSIVE THERAPY AND ANTIDEPRESSANTS

TABLE IV

HAMILTON RATING SCALE FOR DEPRESSION

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. DEPRESSED MOOD	0 - 4	3	1
2. FEELING OF GUILT	0 - 4	2	0
3. SUICIDE	0 - 4	1	0
4. INSOMNIA - EARLY	0 - 2	1	1
5. INSOMNIA - MIDDLE	0 - 2	1	0
6. INSOMNIA - LATE	0 - 2	1	0
7. WORK AND ACTIVITIES	0 - 4	3	0
8. RETARDATION	0 - 4	0	0
9. AGITATION	0 - 2	2	1
10. ANXIETY PHYSIC	0 - 4	3	2
11. ANXIETY - SOMATIC	0 - 4	2	1
12. ANXIETY SYMPTOMS (G.I.T.)	0 - 2	1	1
13. SOMATIC SYMPTOMS (GEN)	0 - 2	1	0
14. GENITAL SYMPTOMS	0 - 2	0	0
15. HYPOCHONDRIASES	0 - 4	1	0
16. LOSS OF WEIGHT	0 - 2	1	0
17. INSIGHT	0 - 2	1	0
18. DIURNAL VARIATION	0 - 2	2	0
19. DEPERSONALISATION	0 - 4	1	0
20. PARANOID SYMPTOMS	0 - 4	0	0
21. OBSESSIONAL SYMPTOMS	0 - 2	1	1
22. HELPLESSNESS	0 - 4	2	0
23. HOPELESSNESS	0 - 4	3	1
24. WORTHLESSNESS	0 - 4	2	0

PATIENT IDENTIFICATION: 3 SEX: F AGE: 59

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ELECTROCONVULSIVE THERAPY AND ANTIDEPRESSANTS

TABLE V

SERUM PROLACTIN VALUES IN ng/ml.

L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	12.1	4.2
20	0.2	0
40	1.8	0
60	2.9	11.0
90	7.4	0

TABLE VI

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	10.6	6.3
20	15.1	12.2
40	15.3	42.0
60	18.5	62.3
90	23.5	68.8
120	26.3	69.3

PATIENT IDENTIFICATION: 4 SEX: M AGE: 66

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - UNIPOLAR

PHASE: DEPRESSED

TREATMENT: ELECTROCONVULSIVE THERAPY

TABLE VII

HAMILTON RATING SCALE FOR DEPRESSION

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. DEPRESSED MOOD	0 - 4	2	0
2. FEELING OF GUILT	0 - 4	0	0
3. SUICIDE	0 - 4	0	0
4. INSOMNIA - EARLY	0 - 2	0	0
5. INSOMNIA - MIDDLE	0 - 2	0	0
6. INSOMNIA - LATE	0 - 2	1	1
7. WORK AND ACTIVITIES	0 - 4	2	1
8. RETARDATION	0 - 4	2	0
9. AGITATION	0 - 2	0	0
10. ANXIETY PSYCHIC	0 - 4	2	1
11. ANXIETY - SOMATIC	0 - 4	0	0
12. ANXIETY SYMPTOMS (G.I.T.)	0 - 2	1	0
13. SOMATIC SYMPTOMS (GEN)	0 - 2	0	0
14. GENITAL SYMPTOMS	0 - 2	1	0
15. HYPOCHONDRIASES	0 - 4	1	1
16. LOSS OF WEIGHT	0 - 2	1	0
17. INSIGHT	0 - 2	0	0
18. DIURNAL VARIATION	0 - 2	1	0
19. DEPERSONALISATION	0 - 4	0	0
20. PARANOID SYMPTOMS	0 - 4	0	0
21. OBSESSIONAL SYMPTOMS	0 - 2	1	1
22. HELPLESSNESS	0 - 4	1	0
23. HOPELESSNESS	0 - 4	1	0
24. WORTHLESSNESS	0 - 4	0	0

PATIENT IDENTIFICATION: 4 SEX: M AGE: 66

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - UNIPOLAR

PHASE: DEPRESSED

TREATMENT: ELECTROCONVULSIVE THERAPY

TABLE VIII

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	3.8	8.4
20	3.1	4.2
40	0.1	4.5
60	3.8	3.9
90	0	6.6

TABLE IX

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	2.1	6.5
20	4.4	5.4
40	3.6	7.9
60	2.9	4.2
90	7.8	6.0
120	10.8	9.3

PATIENT IDENTIFICATION: 5 SEX: M AGE: 47

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ELECTROCONVULSIVE THERAPY

TABLE X

HAMILTON RATING SCALE FOR DEPRESSION

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. DEPRESSED MOOD	0 - 4	2	0
2. FEELING OF GUILT	0 - 4	0	0
3. SUICIDE	0 - 4	0	0
4. INSOMNIA - EARLY	0 - 2	1	1
5. INSOMNIA - MIDDLE	0 - 2	0	0
6. INSOMNIA - LATE	0 - 2	1	1
7. WORK AND ACTIVITIES	0 - 4	2	0
8. RETARDATION	0 - 4	1	0
9. AGITATION	0 - 2	1	0
10. ANXIETY PSYCHIC	0 - 4	2	1
11. ANXIETY - SOMATIC	0 - 4	0	0
12. ANXIETY SYMPTOMS (G.I.T.)	0 - 2	0	0
13. SOMATIC SYMPTOMS (GEN)	0 - 2	1	0
14. GENITAL SYMPTOMS	0 - 2	1	0
15. HYPOCHONDRIASES	0 - 4	0	0
16. LOSS OF WEIGHT	0 - 2	2	1
17. INSIGHT	0 - 2	0	0
18. DIURNAL VARIATION	0 - 2	0	0
19. DEPERSONALISATION	0 - 4	0	0
20. PARANOID SYMPTOMS	0 - 4	0	0
21. OBSESSIONAL SYMPTOMS	0 - 2	0	0
22. HELPLESSNESS	0 - 4	0	0
23. HOPELESSNESS	0 - 4	1	1
24. WORTHLESSNESS	0 - 4	1	0

PATIENT IDENTIFICATION: 5 SEX: M AGE: 47

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ELECTROCONVULSIVE THERAPY

TABLE XI

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	9.0	12.8
20	7.8	8.9
40		1.3
60	6.6	3.0
90	5.2	3.3

TABLE XII

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	12.3	13.2
20	9.7	10.8
40	10.4	18.7
60	23.1	26.6
90	21.4	28.7
120	16.5	24.1

PATIENT IDENTIFICATION: 6 SEX: F AGE: 75

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - UNIPOLAR

PHASE: DEPRESSED

TREATMENT: ELECTROCONVULSIVE THERAPY

TABLE XIII

HAMILTON RATING SCALE FOR DEPRESSION

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. DEPRESSED MOOD	0 - 4	3	1
2. FEELING OF GUILT	0 - 4	0	0
3. SUICIDE	0 - 4	1	0
4. INSOMNIA - EARLY	0 - 2	0	0
5. INSOMNIA - MIDDLE	0 - 2	0	0
6. INSOMNIA - LATE	0 - 2	1	1
7. WORK AND ACTIVITIES	0 - 4	2	1
8. RETARDATION	0 - 4	0	0
9. AGITATION	0 - 2	2	0
10. ANXIETY PSYCHIC	0 - 4	2	1
11. ANXIETY SOMATIC	0 - 4	0	0
12. ANXIETY SYMPTOMS (G.I.T.)	0 - 2	2	1
13. SOMATIC SYMPTOMS (GEN)	0 - 2	0	0
14. GENITAL SYMPTOMS	0 - 2	0	0
15. HYPOCHONDRIASES	0 - 4	0	0
16. LOSS OF WEIGHT	0 - 2	1	0
17. INSIGHT	0 - 2	0	0
18. DIURNAL VARIATION	0 - 2	2	1
19. DEPERSONALISATION	0 - 4	0	0
20. PARANOID SYMPTOMS	0 - 4	0	0
21. OBSESSIONAL SYMPTOMS	0 - 2	2	1
22. HELPLESSNESS	0 - 4	2	0
23. HOPELESSNESS	0 - 4	2	1
24. WORTHLESSNESS	0 - 4	1	0

PATIENT IDENTIFICATION: 6 SEX: F AGE: 75

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - UNIPOLAR

TREATMENT: ELECTROCONVULSIVE THERAPY

TABLE XIV

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	10.6	6.8
20	3.9	4.6
40	7.5	3.3
60	13.5	
90	9.4	3.0

TABLE XV

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	10.7	22.9
20	9.9	14.7
40	10.0	12.0
60	9.1	14.4
90	11.9	17.1
120	16.2	18.9

PATIENT IDENTIFICATION : 7 SEX: F AGE: 67

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ELECTROCONVULSIVE THERAPY

TABLE XVI

HAMILTON RATING SCALE FOR DEPRESSION

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. DEPRESSED MOOD	0 - 4	3	1
2. FEELING OF GUILT	0 - 4	3	0
3. SUICIDE	0 - 4	3	0
4. INSOMNIA - EARLY	0 - 2	1	0
5. INSOMNIA - MIDDLE	0 - 2	1	0
6. INSOMNIA - LATE	0 - 2	2	1
7. WORK AND ACTIVITIES	0 - 4	3	1
8. RETARDATION	0 - 4	3	0
9. AGITATION	0 - 2	0	0
10. ANXIETY PSYCHIC	0 - 4	2	1
11. ANXIETY - SOMATIC	0 - 4	0	0
12. ANXIETY SYMPTOMS (G.I.T.)	0 - 2	1	0
13. SOMATIC SYMPTOMS (GEN)	0 - 2	0	0
14. GENITAL SYMPTOMS	0 - 2	2	1
15. HYPOCHONDRIASES	0 - 4	1	0
16. LOSS OF WEIGHT	0 - 2	1	0
17. INSIGHT	0 - 2	2	0
18. DIURNAL VARIATION	0 - 2	2	0
19. DEPERSONALISATION	0 - 4	3	0
20. PARANOID SYMPTOMS	0 - 4	0	0
21. OBSESSIONAL SYMPTOMS	0 - 2	0	2
22. HELPLESSNESS	0 - 4	3	1
23. HOPELESSNESS	0 - 4	3	0
24. WORTHLESSNESS	0 - 4	4	1

PATIENT IDENTIFICATION: 7 SEX: F AGE: 67

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

TREATMENT: ELECTROCONVULSIVE THERAPY

TABLE XVII

SERUM PROLACTIN VALUES IN ng/ml
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	5.7	0.3
20	3.2	0
40	3.6	3.9
60	4.5	0
90	3.5	0

TABLE XVIII

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	7.5	20.0
20	6.1	7.9
40	8.1	28.5
60	9.1	27.5
90	18.9	37.6
120	13.8	41.5

PATIENT IDENTIFICATION: 8 SEX: F AGE: 41

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ANTIDEPRESSANTS

TABLE XIX

HAMILTON RATING SCALE FOR DEPRESSION

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. DEPRESSED MOOD	0 - 4	3	0
2. FEELING OF GUILT	0 - 4	1	1
3. SUICIDE	0 - 4	2	0
4. INSOMNIA - EARLY	0 - 2	2	1
5. INSOMNIA - MIDDLE	0 - 2	1	0
6. INSOMNIA - LATE	0 - 2	2	0
7. WORK AND ACTIVITIES	0 - 4	2	1
8. RETARDATION	0 - 4	1	0
9. AGITATION	0 - 2	2	0
10. ANXIETY PSYCHIC	0 - 4	3	2
11. ANXIETY - SOMATIC	0 - 4	1	0
12. ANXIETY SYMPTOMS (G.I.T.)	0 - 2	1	1
13. SOMATIC SYMPTOMS (GEN)	0 - 2	0	0
14. GENITAL SYMPTOMS	0 - 2	1	0
15. HYPOCHONDRIASES	0 - 4	0	0
16. LOSS OF WEIGHT	0 - 2	1	0
17. INSIGHT	0 - 2	0	0
18. DIURNAL VARIATION	0 - 2	1	0
19. DEPERSONALISATION	0 - 4	0	0
20. PARANOID SYMPTOMS	0 - 4	1	0
21. OBSESSIONAL SYMPTOMS	0 - 2	0	1
22. HELPLESSNESS	0 - 4	2	0
23. HOPELESSNESS	0 - 4	2	1
24. WORTHLESSNESS	0 - 4	2	1

PATIENT IDENTIFICATION: 8 SEX: F AGE: 41

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ANTIDEPRESSANTS

TABLE XX

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	12.7	10.1
20	6.3	7.0
40	5.2	6.9
60	3.8	6.0
90	6.5	6.2

TABLE XXI

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	8.6	6.2
20	13.1	7.2
40	13.9	8.7
60	17.8	10.4
90	26.5	18.0
120		35.4

PATIENT IDENTIFICATION: 9 SEX: F AGE: 54

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ELECTROCONVULSIVE THERAPY

TABLE XXII

HAMILTON RATING SCALE FOR DEPRESSION

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. DEPRESSED MOOD	0 - 4	3	1
2. FEELING OF GUILT	0 - 4	2	0
3. SUICIDE	0 - 4	0	0
4. INSOMNIA - EARLY	0 - 2	1	0
5. INSOMNIA - MIDDLE	0 - 2	0	0
6. INSOMNIA - LATE	0 - 2	1	0
7. WORK AND ACTIVITIES	0 - 4	3	0
8. RETARDATION	0 - 4	3	0
9. AGITATION	0 - 2	2	1
10. ANXIETY PSYCHIC	0 - 4	2	0
11. ANXIETY - SOMATIC	0 - 4	2	0
12. ANXIETY SYMPTOMS (G.I.T.)	0 - 2	0	0
13. SOMATIC SYMPTOMS (GEN)	0 - 2	1	0
14. GENITAL SYMPTOMS	0 - 2	2	0
15. HYPOCHONDRIASES	0 - 4	2	0
16. LOSS OF WEIGHT	0 - 2	0	0
17. INSIGHT	0 - 2	1	1
18. DIURNAL VARIATION	0 - 2	0	0
19. DEPERSONALISATION	0 - 4	0	0
20. PARANOID SYMPTOMS	0 - 4	0	0
21. OBSESSIONAL SYMPTOMS	0 - 2	0	0
22. HELPLESSNESS	0 - 4	2	0
23. HOPELESSNESS	0 - 4	3	0
24. WORTHLESSNESS	0 - 4	2	1

PATIENT IDENTIFICATION: 9 SEX: F AGE: 54

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ELECTROCONVULSIVE THERAPY

TABLE XXIII

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	0	8.7
20	0	0.9
40	0	2.1
60	0	0
90	0	0

TABLE XXIV

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	0	10.2
20	0	8.1
40	0	9.5
60	0	14.8
90	0.9	
120	3.1	21.6

PATIENT IDENTIFICATION: 10 SEX: F AGE: 48

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - UNIPOLAR

PHASE: DEPRESSED

TREATMENT: ANTIDEPRESSANTS

TABLE XXV

HAMILTON RATING SCALE FOR DEPRESSION

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. DEPRESSED MOOD	0 - 4	2	1
2. FEELING OF GUILT	0 - 4	0	0
3. SUICIDE	0 - 4	2	0
4. INSOMNIA - EARLY	0 - 2	1	1
5. INSOMNIA - MIDDLE	0 - 2	1	0
6. INSOMNIA - LATE	0 - 2	1	0
7. WORK AND ACTIVITIES	0 - 4	2	1
8. RETARDATION	0 - 4	0	0
9. AGITATION	0 - 2	0	0
10. ANXIETY PSYCHIC	0 - 4	2	2
11. ANXIETY - SOMATIC	0 - 4	0	0
12. ANXIETY SYMPTOMS (G.I.T.)	0 - 2	1	1
13. SOMATIC SYMPTOMS (GEN)	0 - 2	1	0
14. GENITAL SYMPTOMS	0 - 2	0	0
15. HYPOCHONDRIASES	0 - 4	0	0
16. LOSS OF WEIGHT	0 - 2	1	0
17. INSIGHT	0 - 2	0	0
18. DIURNAL VARIATION	0 - 2	2	0
19. DEPERSONALISATION	0 - 4	0	0
20. PARANOID SYMPTOMS	0 - 4	0	0
21. OBSESSIONAL SYMPTOMS	0 - 2	0	0
22. HELPLESSNESS	0 - 4	1	1
23. HOPELESSNESS	0 - 4	1	0
24. WORTHLESSNESS	0 - 4	1	0

PATIENT IDENTIFICATION: 10 SEX: F AGE: 48

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - UNIPOLAR

PHASE: DEPRESSED

TREATMENT: ANTIDEPRESSANTS

TABLE XXVI

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	7.6	11.5
20	6.3	7.0
40	8.5	5.3
60	7.1	8.4
90	5.7	4.2

TABLE XXVII

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	7.4	12.8
20	8.5	9.0
40	9.2	10.3
60	10.1	10.8
90	15.3	17.1
120	14.9	9.5

PATIENT IDENTIFICATION: 11 SEX: M AGE: 23

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ANTIDEPRESSANTS

TABLE XXVIII

HAMILTON RATING SCALE FOR DEPRESSION

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. DEPRESSED MOOD	0 - 4	2	0
2. FEELING OF GUILT	0 - 4	3	0
3. SUICIDE	0 - 4	1	0
4. INSOMNIA - EARLY	0 - 2	1	0
5. INSOMNIA - MIDDLE	0 - 2	0	0
6. INSOMNIA - LATE	0 - 2	0	0
7. WORK AND ACTIVITIES	0 - 4	2	0
8. RETARDATION	0 - 4	1	0
9. AGITATION	0 - 2	1	0
10. ANXIETY PSYCHIC	0 - 4	2	1
11. ANXIETY - SOMATIC	0 - 4	0	0
12. ANXIETY SYMPTOMS (G.I.T.)	0 - 2	0	0
13. SOMATIC SYMPTOMS (GEN)	0 - 2	1	0
14. GENITAL SYMPTOMS	0 - 2	0	0
15. HYPOCHONDRIASES	0 - 4	1	0
16. LOSS OF WEIGHT	0 - 2	0	0
17. INSIGHT	0 - 2	0	0
18. DIURNAL VARIATION	0 - 2	1	0
19. DEPERSONALISATION	0 - 4	0	0
20. PARANOID SYMPTOMS	0 - 4	0	0
21. OBSESSIONAL SYMPTOMS	0 - 2	1	0
22. HELPLESSNESS	0 - 4	1	0
23. HOPELESSNESS	0 - 4	2	0
24. WORTHLESSNESS	0 - 4	1	0

PATIENT IDENTIFICATION: 11 SEX: M AGE: 23

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ANTIDEPRESSANTS

TABLE XXIX

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	11.4	1.7
20	5.7	0
40	0	0
60	0	0
90	0	0

TABLE XXX

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	4.7	1.4
20	1.2	3.1
40	2.5	5.6
60	6.9	13.5
90	8.0	11.2
120	9.1	14.9

PATIENT IDENTIFICATION: 14 SEX: M AGE: 67

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ANTIDEPRESSANTS

TABLE XXXI

HAMILTON RATING SCALE FOR DEPRESSION

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. DEPRESSED MOOD	0 - 4	3	1
2. FEELING OF GUILT	0 - 4	1	0
3. SUICIDE	0 - 4	1	0
4. INSOMNIA - EARLY	0 - 2	1	1
5. INSOMNIA - MIDDLE	0 - 2	0	0
6. INSOMNIA - LATE	0 - 2	0	1
7. WORK AND ACTIVITIES	0 - 4	3	0
8. RETARDATION	0 - 4	3	0
9. AGITATION	0 - 2	0	0
10. ANXIETY PSYCHIC	0 - 4	2	0
11. ANXIETY - SOMATIC	0 - 4	1	0
12. ANXIETY SYMPTOMS (G.I.T.)	0 - 2	2	0
13. SOMATIC SYMPTOMS (GEN)	0 - 2	0	0
14. GENITAL SYMPTOMS	0 - 2	1	1
15. HYPOCHONDRIASES	0 - 4	1	0
16. LOSS OF WEIGHT	0 - 2	1	0
17. INSIGHT	0 - 2	1	1
18. DIURNAL VARIATION	0 - 2	1	0
19. DEPERSONALISATION	0 - 4	2	0
20. PARANOID SYMPTOMS	0 - 4	1	0
21. OBSESSIONAL SYMPTOMS	0 - 2	0	0
22. HELPLESSNESS	0 - 4	2	0
23. HOPELESSNESS	0 - 4	2	1
24. WORTHLESSNESS	0 - 4	2	0

PATIENT IDENTIFICATION: 14 SEX: M AGE: 67

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ANTIDEPRESSANTS

TABLE XXXII

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	0	5.1
20	0	1.5
40	0	0
60	0	0
90	0	0

TABLE XXXIII

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	0	7.7
20	0	3.7
40	0	1.5
60	0	3.4
90	0	
120	0	

PATIENT IDENTIFICATION: 15 SEX: F AGE: 58

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ELECTROCONVULSIVE THERAPY

TABLE XXXIV

HAMILTON RATING SCALE FOR DEPRESSION

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. DEPRESSED MOOD	0 - 4	3	0
2. FEELING OF GUILT	0 - 4	3	0
3. SUICIDE	0 - 4	3	0
4. INSOMNIA - EARLY	0 - 2	0	1
5. INSOMNIA - MIDDLE	0 - 2	2	1
6. INSOMNIA - LATE	0 - 2	2	0
7. WORK AND ACTIVITIES	0 - 4	3	0
8. RETARDATION	0 - 4	3	0
9. AGITATION	0 - 2	1	0
10. ANXIETY PSYCHIC	0 - 4	3	1
11. ANXIETY - SOMATIC	0 - 4	0	0
12. ANXIETY SYMPTOMS (G.I.T.)	0 - 2	0	1
13. SOMATIC SYMPTOMS (GEN)	0 - 2	1	1
14. GENITAL SYMPTOMS	0 - 2	2	0
15. HYPOCHONDRIASES	0 - 4	0	0
16. LOSS OF WEIGHT	0 - 2	1	0
17. INSIGHT	0 - 2	1	0
18. DIURNAL VARIATION	0 - 2	0	0
19. DEPERSONALISATION	0 - 4	2	0
20. PARANOID SYMPTOMS	0 - 4	2	0
21. OBSESSIONAL SYMPTOMS	0 - 2	1	0
22. HELPLESSNESS	0 - 4	3	0
23. HOPELESSNESS	0 - 4	4	0
24. WORTHLESSNESS	0 - 4	3	0

PATIENT IDENTIFICATION: 15 SEX: F AGE: 58

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ELECTROCONVULSIVE THERAPY

TABLE XXXV

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	18.1	49.8
20	9.7	25.3
40	7.3	33.2
60	7.8	30.7
90	12.0	41.5

TABLE XXXVI

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	13.5	22.7
20	12.2	21.5
40	14.3	16.7
60	21.9	26.9
90	19.8	
120	16.0	14.3

PATIENT IDENTIFICATION: 16 SEX: M AGE: 55

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ELECTROCONVULSIVE THERAPY

TABLE XXXVII

HAMILTON RATING SCALE FOR DEPRESSION

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. DEPRESSED MOOD	0 - 4	3	1
2. FEELING OF GUILT	0 - 4	0	0
3. SUICIDE	0 - 4	1	0
4. INSOMNIA - EARLY	0 - 2	0	0
5. INSOMNIA - MIDDLE	0 - 2	1	0
6. INSOMNIA - LATE	0 - 2	1	0
7. WORK AND ACTIVITIES	0 - 4	2	1
8. RETARDATION	0 - 4	1	0
9. AGITATION	0 - 2	0	0
10. ANXIETY PHYSIC	0 - 4	2	0
11. ANXIETY - SOMATIC	0 - 4	0	0
12. ANXIETY SYMPTOMS (G.I.T.)	0 - 2	0	0
13. SOMATIC SYMPTOMS (GEN)	0 - 2	0	0
14. GENITAL SYMPTOMS	0 - 2	1	1
15. HYPOCHONDRIASES	0 - 4	2	2
16. LOSS OF WEIGHT	0 - 2	1	0
17. INSIGHT	0 - 2	0	0
18. DIURNAL VARIATION	0 - 2	1	1
19. DEPERSONALISATION	0 - 4	0	0
20. PARANOID SYMPTOMS	0 - 4	0	0
21. OBSESSIONAL SYMPTOMS	0 - 2	0	0
22. HELPLESSNESS	0 - 4	1	0
23. HOPELESSNESS	0 - 4	2	1
24. WORTHLESSNESS	0 - 4	2	1

PATIENT IDENTIFICATION: 16 SEX: M AGE: 55

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ELECTROCONVULSIVE THERAPY

TABLE XXXVIII

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	0.6	2.8
20	0	1.3
40	0	1.1
60	0	2.1
90	0	2.0

TABLE XXXIX

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	0.4	5.0
20	4.2	5.2
40	7.4	6.1
60	7.5	13.0
90	9.1	12.2
120	9.8	12.8

PATIENT IDENTIFICATION: 17 SEX: F AGE: 52

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ANTIDEPRESSANTS

TABLE XL

HAMILTON RATING SCALE FOR DEPRESSION

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. DEPRESSED MOOD	0 - 4	3	0
2. FEELING OF GUILT	0 - 4	2	1
3. SUICIDE	0 - 4	1	0
4. INSOMNIA - EARLY	0 - 2	0	0
5. INSOMNIA - MIDDLE	0 - 2	0	0
6. INSOMNIA - LATE	0 - 2	2	1
7. WORK AND ACTIVITIES	0 - 4	3	1
8. RETARDATION	0 - 4	2	0
9. AGITATION	0 - 2	1	0
10. ANXIETY PSYCHIC	0 - 4	3	2
11. ANXIETY - SOMATIC	0 - 4	1	0
12. ANXIETY SYMPTOMS (G.I.T.)	0 - 2	0	0
13. SOMATIC SYMPTOMS (GEN)	0 - 2	2	1
14. GENITAL SYMPTOMS	0 - 2	1	1
15. HYPOCHONDRIASES	0 - 4	2	1
16. LOSS OF WEIGHT	0 - 2	2	0
17. INSIGHT	0 - 2	1	0
18. DIURNAL VARIATION	0 - 2	0	0
19. DEPERSONALISATION	0 - 4	0	0
20. PARANOID SYMPTOMS	0 - 4	2	0
21. OBSESSIONAL SYMPTOMS	0 - 2	1	0
22. HELPLESSNESS	0 - 4	2	0
23. HOPELESSNESS	0 - 4	2	0
24. WORTHLESSNESS	0 - 4	2	1

PATIENT IDENTIFICATION: 17 SEX: F AGE: 52

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ANTIDEPRESSANTS

TABLE XLI

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	5.9	9.9
20	4.0	8.0
40	3.8	7.2
60	5.5	7.8
90	4.7	11.1

TABLE XLII

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	6.3	12.5
20	10.7	10.9
40	19.1	13.9
60	20.9	
90	16.5	23.9
120	21.6	27.7

PATIENT IDENTIFICATION: 18 SEX: M AGE: 61

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - UNIPOLAR

PHASE: DEPRESSED

TREATMENT: ANTIDEPRESSANTS

TABLE XLIII

HAMILTON RATING SCALE FOR DEPRESSION

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. DEPRESSED MOOD	0 - 4	3	1
2. FEELING OF GUILT	0 - 4	0	0
3. SUICIDE	0 - 4	1	1
4. INSOMNIA - EARLY	0 - 2	2	0
5. INSOMNIA - MIDDLE	0 - 2	0	0
6. INSOMNIA - LATE	0 - 2	1	0
7. WORK AND ACTIVITIES	0 - 4	2	1
8. RETARDATION	0 - 4	2	1
9. AGITATION	0 - 2	1	1
10. ANXIETY PSYCHIC	0 - 4	3	3
11. ANXIETY - SOMATIC	0 - 4	1	0
12. ANXIETY SYMPTOMS (G.I.T.)	0 - 2	1	0
13. SOMATIC SYMPTOMS (GEN)	0 - 2	1	0
14. GENITAL SYMPTOMS	0 - 2	2	2
15. HYPOCHONDRIASES	0 - 4	2	2
16. LOSS OF WEIGHT	0 - 2	1	0
17. INSIGHT	0 - 2	0	0
18. DIURNAL VARIATION	0 - 2	1	0
19. DEPERSONALISATION	0 - 4	0	0
20. PARANOID SYMPTOMS	0 - 4	0	0
21. OBSESSIONAL SYMPTOMS	0 - 2	0	0
22. HELPLESSNESS	0 - 4	2	0
23. HOPELESSNESS	0 - 4	2	2
24. WORTHLESSNESS	0 - 4	1	1

PATIENT IDENTIFICATION: 18 SEX: M AGE: 61

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - UNIPOLAR

PHASE: DEPRESSED

TREATMENT: ANTIDEPRESSANTS

TABLE XLIV

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGES

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	2.8	3.5
20	0	2.6
40	0	0.8
60	0	0.9
90	0	3.1

TABLE XLV

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	2.5	6.1
20	0	3.9
40	2.3	4.3
60	3.2	5.7
90	0.9	5.3
120	9.7	7.2

PATIENT IDENTIFICATION: 19 SEX: F AGE: 53

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ELECTROCONVULSIVE THERAPY

TABLE XLVI

HAMILTON RATING SCALE FOR DEPRESSION

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. DEPRESSED MOOD	0 - 4	4	2
2. FEELING OF GUILT	0 - 4	0	0
3. SUICIDE	0 - 4	0	0
4. INSOMNIA - EARLY	0 - 2	2	2
5. INSOMNIA - MIDDLE	0 - 2	2	1
6. INSOMNIA - LATE	0 - 2	2	2
7. WORK AND ACTIVITIES	0 - 4	4	2
8. RETARDATION	0 - 4	4	2
9. AGITATION	0 - 2	0	0
10. ANXIETY PSYCHIC	0 - 4	0	0
11. ANXIETY - SOMATIC	0 - 4	0	0
12. ANXIETY SYMPTOMS (G.I.T.)	0 - 2	0	0
13. SOMATIC SYMPTOMS (GEN)	0 - 2	1	0
14. GENITAL SYMPTOMS	0 - 2	0	0
15. HYPOCHONDRIASES	0 - 4	0	0
16. LOSS OF WEIGHT	0 - 2	2	1
17. INSIGHT	0 - 2	2	1
18. DIURNAL VARIATION	0 - 2	0	0
19. DEPERSONALISATION	0 - 4	2	0
20. PARANOID SYMPTOMS	0 - 4	0	0
21. OBSESSIONAL SYMPTOMS	0 - 2	0	0
22. HELPLESSNESS	0 - 4	4	3
23. HOPELESSNESS	0 - 4	3	2
24. WORTHLESSNESS	0 - 4	3	2

PATIENT IDENTIFICATION: 19 SEX: F AGE: 53

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ELECTROCONVULSIVE THERAPY

TABLE XLVII

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	8.8	2.9
20	5.9	1.8
40	7.2	3.4
60	6.4	1.5
90	4.7	3.0

TABLE XLVIII

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	17.6	2.6
20	10.7	6.0
40	12.6	8.8
60	14.6	13.3
90	17.1	19.2
120	18.4	28.7

PATIENT IDENTIFICATION: 20 SEX: F AGE: 69

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER

PHASE: DEPRESSED

TREATMENT: ELECTROCONVULSIVE THERAPY

TABLE XLIX

HAMILTON RATING SCALE FOR DEPRESSION

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. DEPRESSED MOOD	0 - 4	2	1
2. FEELING OF GUILT	0 - 4	1	0
3. SUICIDE	0 - 4	1	0
4. INSOMNIA - EARLY	0 - 2	2	1
5. INSOMNIA - MIDDLE	0 - 2	0	0
6. INSOMNIA - LATE	0 - 2	1	0
7. WORK AND ACTIVITIES	0 - 4	2	1
8. RETARDATION	0 - 4	1	0
9. AGITATION	0 - 2	1	1
10. ANXIETY PHYSIC	0 - 4	3	2
11. ANXIETY - SOMATIC	0 - 4	1	0
12. ANXIETY SYMPTOMS (G.I.T.)	0 - 2	0	0
13. SOMATIC SYMPTOMS (GEN)	0 - 2	1	0
14. GENITAL SYMPTOMS	0 - 2	1	0
15. HYPOCHONDRIASES	0 - 4	0	0
16. LOSS OF WEIGHT	0 - 2	2	1
17. INSIGHT	0 - 2	1	0
18. DIURNAL VARIATION	0 - 2	1	1
19. DEPERSONALISATION	0 - 4	0	0
20. PARANOID SYMPTOMS	0 - 4	2	0
21. OBSESSIONAL SYMPTOMS	0 - 2	1	1
22. HELPLESSNESS	0 - 4	2	1
23. HOPELESSNESS	0 - 4	2	1
24. WORTHLESSNESS	0 - 4	1	1

PATIENT IDENTIFICATION: 20 SEX: F AGE: 69

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - UNIPOLAR

PHASE: DEPRESSED

TREATMENT: ELECTROCONVULSIVE THERAPY

TABLE L

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	3.1	2.0
20	2.0	1.1
40	3.4	0.6
60	1.6	0
90	2.1	0.8

TABLE LI

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	3.3	3.1
20	2.2	3.0
40	5.9	6.6
60	10.5	12.9
90	9.7	15.3
120	11.5	11.0

PATIENT IDENTIFICATION: 21 SEX: F AGE: 56

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ANTIDEPRESSANTS

TABLE LII

HAMILTON RATING SCALE FOR DEPRESSION

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. DEPRESSED MOOD	0 - 4	3	0
2. FEELING OF GUILT	0 - 4	3	1
3. SUICIDE	0 - 4	2	0
4. INSOMNIA - EARLY	0 - 2	2	0
5. INSOMNIA - MIDDLE	0 - 2	1	0
6. INSOMNIA - LATE	0 - 2	1	0
7. WORK AND ACTIVITIES	0 - 4	2	0
8. RETARDATION	0 - 4	2	0
9. AGITATION	0 - 2	1	0
10. ANXIETY PSYCHIC	0 - 4	3	1
11. ANXIETY - SOMATIC	0 - 4	1	1
12. ANXIETY SYMPTOMS (G.I.T.)	0 - 2	1	0
13. SOMATIC SYMPTOMS (GEN)	0 - 2	0	0
14. GENITAL SYMPTOMS	0 - 2	2	1
15. HYPOCHONDRIASES	0 - 4	2	1
16. LOSS OF WEIGHT	0 - 2	1	0
17. INSIGHT	0 - 2	2	0
18. DIURNAL VARIATION	0 - 2	2	0
19. DEPERSONALISATION	0 - 4	0	0
20. PARANOID SYMPTOMS	0 - 4	1	0
21. OBSESSIONAL SYMPTOMS	0 - 2	2	2
22. HELPLESSNESS	0 - 4	2	0
23. HOPELESSNESS	0 - 4	2	1
24. WORTHLESSNESS	0 - 4	2	0

PATIENT IDENTIFICATION: 21 SEX: F AGE: 56

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ANTIDEPRESSANTS

TABLE LIII

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	7.2	14.1
20	3.7	9.3
40	2.8	4.7
60	1.9	7.5
90	1.9	6.8

TABLE LIV

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	6.7	17.4
20	6.1	13.5
40	8.0	21.6
60	12.1	19.0
90	16.2	20.7
120	15.2	

PATIENT IDENTIFICATION: 23 SEX: F AGE: 60

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ANTIDEPRESSANTS

TABLE LV

HAMILTON RATING SCALE FOR DEPRESSION

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. DEPRESSED MOOD	0 - 4	2	1
2. FEELING OF GUILT	0 - 4	0	0
3. SUICIDE	0 - 4	1	0
4. INSOMNIA - EARLY	0 - 2	1	1
5. INSOMNIA - MIDDLE	0 - 2	1	0
6. INSOMNIA - LATE	0 - 2	1	1
7. WORK AND ACTIVITIES	0 - 4	2	1
8. RETARDATION	0 - 4	0	0
9. AGITATION	0 - 2	1	0
10. ANXIETY PSYCHIC	0 - 4	2	1
11. ANXIETY - SOMATIC	0 - 4	2	1
12. ANXIETY SYMPTOMS (G.I.T.)	0 - 2	1	0
13. SOMATIC SYMPTOMS (GEN)	0 - 2	0	0
14. GENITAL SYMPTOMS	0 - 2	1	0
15. HYPOCHONDRIASES	0 - 4	0	0
16. LOSS OF WEIGHT	0 - 2	1	1
17. INSIGHT	0 - 2	1	0
18. DIURNAL VARIATION	0 - 2	0	0
19. DEPERSONALISATION	0 - 4	0	0
20. PARANOID SYMPTOMS	0 - 4	2	0
21. OBSESSIONAL SYMPTOMS	0 - 2	0	0
22. HELPLESSNESS	0 - 4	0	0
23. HOPELESSNESS	0 - 4	1	1
24. WORTHLESSNESS	0 - 4	1	0

PATIENT IDENTIFICATION: 22 SEX: F AGE: 60

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ANTIDEPRESSANTS

TABLE LVI

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	7.2	5.8
20	3.8	3.5
40	3.3	0
60	2.8	0.9
90	2.7	3.2

TABLE LVII

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	3.9	6.2
20	5.7	4.0
40	7.1	9.2
60	13.6	15.4
90	16.4	16.5
120	17.7	14.2

PATIENT IDENTIFICATION: 23 SEX: F AGE: 70

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ELECTROCONVULSIVE THERAPY

TABLE LVIII

HAMILTON RATING SCALE FOR DEPRESSION

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. DEPRESSED MOOD	0 - 4	3	1
2. FEELING OF GUILT	0 - 4	1	0
3. SUICIDE	0 - 4	2	0
4. INSOMNIA - EARLY	0 - 2	1	1
5. INSOMNIA - MIDDLE	0 - 2	1	0
6. INSOMNIA - LATE	0 - 2	1	0
7. WORK AND ACTIVITIES	0 - 4	3	1
8. RETARDATION	0 - 4	3	1
9. AGITATION	0 - 2	0	0
10. ANXIETY PSYCHIC	0 - 4	1	1
11. ANXIETY - SOMATIC	0 - 4	0	0
12. ANXIETY SYMPTOMS (G.I.T.)	0 - 2	1	1
13. SOMATIC SYMPTOMS (GEN)	0 - 2	1	0
14. GENITAL SYMPTOMS	0 - 2	0	0
15. HYPOCHONDRIASES	0 - 4	1	0
16. LOSS OF WEIGHT	0 - 2	1	2
17. INSIGHT	0 - 2	1	0
18. DIURNAL VARIATION	0 - 2	0	0
19. DEPERSONALISATION	0 - 4	0	0
20. PARANOID SYMPTOMS	0 - 4	2	0
21. OBSESSIONAL SYMPTOMS	0 - 2	0	0
22. HELPLESSNESS	0 - 4	3	1
23. HOPELESSNESS	0 - 4	3	1
24. WORTHLESSNESS	0 - 4	2	0

PATIENT IDENTIFICATION: 23 SEX: F AGE: 70

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: DEPRESSED

TREATMENT: ELECTROCONVULSIVE THERAPY

TABLE LIX

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	13.2	33.0
20	10.8	17.0
40	9.6	17.7
60	10.3	14.9
90	7.4	10.8

TABLE LX

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	13.1	34.0
20	9.6	32.9
40	10.3	25.9
60	13.3	29.6
90		34.1
120	15.1	21.6

PATIENT IDENTIFICATION: 25 SEX: F AGE: 65

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - UNIPOLAR

PHASE: DEPRESSED

TREATMENT: ANTIDEPRESSANTS

TABLE LXI

HAMILTON RATING SCALE FOR DEPRESSION

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. DEPRESSED MOOD	0 - 4	3	1
2. FEELING OF GUILT	0 - 4	3	1
3. SUICIDE	0 - 4	2	0
4. INSOMNIA - EARLY	0 - 2	1	0
5. INSOMNIA - MIDDLE	0 - 2	0	0
6. INSOMNIA - LATE	0 - 2	1	0
7. WORK AND ACTIVITIES	0 - 4	2	1
8. RETARDATION	0 - 4	0	0
9. AGITATION	0 - 2	2	0
10. ANXIETY PSYCHIC	0 - 4	2	1
11. ANXIETY - SOMATIC	0 - 4	2	1
12. ANXIETY SYMPTOMS (G.I.T.)	0 - 2	1	1
13. SOMATIC SYMPTOMS (GEN)	0 - 2	1	1
14. GENITAL SYMPTOMS	0 - 2	1	0
15. HYPOCHONDRIASES	0 - 4	3	2
16. LOSS OF WEIGHT	0 - 2	0	0
17. INSIGHT	0 - 2	2	0
18. DIURNAL VARIATION	0 - 2	0	0
19. DEPERSONALISATION	0 - 4	0	0
20. PARANOID SYMPTOMS	0 - 4	3	0
21. OBSESSIONAL SYMPTOMS	0 - 2	1	1
22. HELPLESSNESS	0 - 4	1	0
23. HOPELESSNESS	0 - 4	1	0
24. WORTHLESSNESS	0 - 4	3	1

PATIENT IDENTIFICATION: 25 SEX: F AGE: 65

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - UNIPOLAR

PHASE: DEPRESSED

TREATMENT: ANTIDEPRESSANTS

TABLE LXII

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	5.1	6.9
20	3.7	5.4
40	2.5	2.0
60	2.8	2.1
90	2.1	3.0

TABLE LXIII

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	5.7	7.5
20	5.9	6.3
40	10.0	11.1
60	15.7	17.0
90	20.3	21.8
120	17.5	21.0

PATIENT IDENTIFICATION: 2 SEX: F AGE: 19

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: MANIC

TREATMENT: NEUROLEPTICS

TABLE LXIV

PETTERSEN RATING SCALE FOR MANIA

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. MOTOR ACTIVITY	1 - 5	4	1
2. PRESSURE OF SPEECH	1 - 5	3	2
3. FLIGHT OF IDEAS	1 - 5	2	1
4. NOISINESS	1 - 5	2	1
5. AGGRESSIVENESS	1 - 5	2	1
6. ORIENTATION	1 - 3	1	1
7. ELEVATED MOOD	1 - 5	3	1
8. GLOBAL RATING OF MANIA	1 - 5	3	1
	TOTAL	20	9

PATIENT IDENTIFICATION: 2 SEX: F AGE: 19

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: MANIC

TREATMENT: NEUROLEPTICS

TABLE LXV

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	27.9	8.6
20	4.3	3.2
40	0	2.5
60	0	3.5
90	4.9	3.6

TABLE LXVI

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	32.5	7.0
20	52.9	13.5
40	90.6	20.5
60	120.8	53.4
90	102.2	81.6
120	126.0	51.3

PATIENT IDENTIFICATION: 9 SEX: F AGE: 54

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: MANIC

TREATMENT: NEUROLEPTICS

TABLE LXVII

PETTERSEN RATING SCALE FOR MANIA

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. MOTOR ACTIVITY	1 - 5	2	1
2. PRESSURE OF SPEECH	1 - 5	2	1
3. FLIGHT OF IDEAS	1 - 5	1	1
4. NOISINESS	1 - 5	2	1
5. AGGRESSIVENESS	1 - 5	2	1
6. ORIENTATION	1 - 3	1	1
7. ELEVATED MOOD	1 - 5	2	1
8. GLOBAL RATING OF MANIA	1 - 5	2	1
	TOTAL	14	8

PATIENT IDENTIFICATION: 9 SEX: F AGE: 54

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: MANIC

TREATMENT: NEUROLEPTICS

TABLE LXVIII

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	25.8	8.7
20	13.0	0.9
40	8.3	2.1
60	6.6	0
90	6.4	0

TABLE LXIX

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	27.1	10.2
20	30.6	8.1
40	56.2	9.5
60	76.5	14.8
90	127.2	
120	120.5	21.6

PATIENT IDENTIFICATION: 13 SEX: F AGE: 32

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: MANIC

TREATMENT: NEUROLEPTICS

TABLE LXX

PETTERSEN RATING SCALE FOR MANIA

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. MOTOR ACTIVITY	1 - 5	3	2
2. PRESSURE OF SPEECH	1 - 5	2	1
3. FLIGHT OF IDEAS	1 - 5	2	1
4. NOISINESS	1 - 5	1	1
5. AGGRESSIVENESS	1 - 5	3	1
6. ORIENTATION	1 - 3	1	1
7. ELEVATED MOOD	1 - 5	2	1
8. GLOBAL RATING OF MANIA	1 - 5	3	1
	TOTAL	17	9

PATIENT IDENTIFICATION: 13 SEX: F AGE: 32

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: MANIC

TREATMENT: NEUROLEPTICS

TABLE LXXI

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	9.9	8.9
20	2.7	3.7
40	2.0	2.6
60	0.1	3.3
90	2.0	2.8

TABLE LXXII

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	8.2	6.7
20	10.6	8.8
40	16.3	13.1
60	27.4	16.9
90	17.2	19.9
120		23.0

PATIENT IDENTIFICATION: 14 SEX: M AGE: 62

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: MANIC

TREATMENT: NEUROLEPTICS

TABLE LXXIII

PETTERSEN RATING SCALE OF MANIA

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. MOTOR ACTIVITY	1 - 5	2	1
2. PRESSURE OF SPEECH	1 - 5	3	2
3. FLIGHT OF IDEAS	1 - 5	2	1
4. NOISINESS	1 - 5	2	1
5. AGGRESSIVENESS	1 - 5	2	1
6. ORIENTATION	1 - 3	1	1
7. ELEVATED MOOD	1 - 5	3	1
8. GLOBAL RATING OF MANIA	1 - 5	3	1
	TOTAL	18	9

PATIENT IDENTIFICATION: 14 SEX: M AGE: 62

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: MANIC

TREATMENT: NEUROLEPTICS

TABLE LXXXIV

SERUM PROLACTIN VALUES IN ng/ml
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	11.0	7.5
20	4.5	0
40	4.4	1.5
60	3.8	4.1
90	5.0	0.9

TABLE LXXV

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	8.8	8.0
20	10.2	6.9
40	9.1	1.2
60	11.3	10.5
90	14.9	16.8
120	19.9	25.1

PATIENT IDENTIFICATION: 19 SEX: F AGE: 53

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: MANIC

TREATMENT: NEUROLEPTICS

TABLE LXXVI

PETTERSEN RATING SCALE FOR MANIA

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. MOTOR ACTIVITY	1 - 5	2	1
2. PRESSURE OF SPEECH	1 - 5	2	1
3. FLIGHT OF IDEAS	1 - 5	1	1
4. NOISINESS	1 - 5	2	1
5. AGGRESSIVENESS	1 - 5	1	1
6. ORIENTATION	1 - 3	1	1
7. ELEVATED MOOD	1 - 5	2	1
8. GLOBAL RATING OF MANIA	1 - 5	2	1
	TOTAL	13	8

PATIENT IDENTIFICATION: 19 SEX: F AGE: 53

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: MANIC

TREATMENT: NEUROLEPTICS

TABLE LXXVII

SERUM PROLACTIN VALUES IN ng/ml
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	11.4	2.9
20	11.3	1.8
40	10.9	3.4
60	10.8	1.5
90	7.7	3.0

TABLE LXXVIII

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	18.4	2.6
20	15.1	6.0
40	13.8	8.8
60	19.7	13.3
90	16.7	19.2
120	16.1	28.7

PATIENT IDENTIFICATION: 24 SEX: M AGE: 79

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: MANIC

TREATMENT: NEUROLEPTICS

TABLE LXXIX

PETTERSEN RATING SCALE FOR MANIA

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. MOTOR ACTIVITY	1 - 5	2	1
2. PRESSURE OF SPEECH	1 - 5	3	2
3. FLIGHT OF IDEAS	1 - 5	3	1
4. NOISINESS	1 - 5	3	1
5. AGGRESSIVENESS	1 - 5	2	2
6. ORIENTATION	1 - 3	1	1
7. ELEVATED MOOD	1 - 5	3	1
8. GLOBAL RATING OF MANIA	1 - 5	3	2
	TOTAL	20	11

PATIENT IDENTIFICATION: 24 SEX: M AGE: 79

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: MANIC

TREATMENT: NEUROLEPTICS

TABLE LXXX

SERUM PROLACTIN VALUES IN ng/ml
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	3.1	6.0
20	2.5	5.3
40	2.2	5.3
60	2.6	5.8
90	2.3	5.9

TABLE LXXXI

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	3.6	6.1
20	4.4	5.9
40	5.0	6.7
60	7.0	7.1
90	7.0	5.9
120	13.0	

PATIENT IDENTIFICATION: 26 SEX: F AGE: 21

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: MANIC

TREATMENT: NEUROLEPTICS

TABLE LXXXII

PETTERSEN RATING SCALE FOR MANIA

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. MOTOR ACTIVITY	1 - 5	3	1
2. PRESSURE OF SPEECH	1 - 5	3	1
3. FLIGHT OF IDEAS	1 - 5	2	1
4. NOISINESS	1 - 5	2	1
5. AGGRESSIVENESS	1 - 5	3	1
6. ORIENTATION	1 - 3	1	1
7. ELEVATED MOOD	1 - 5	3	1
8. GLOBAL RATING OF MANIA	1 - 5	3	1
	TOTAL	20	8

PATIENT IDENTIFICATION: 26 SEX: F AGE: 21

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: MANIC

TREATMENT: NEUROLEPTICS

TABLE LXXXIII

SERUM PROLACTIN VALUES IN ng/ml
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	38.8	2.0
20	15.2	0.7
40	13.8	0.3
60	10.2	1.9
90	6.8	2.6

TABLE LXXXIV

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	22.3	2.0
20	40.0	1.2
40	76.3	1.9
60	107.0	0.6
90	151.2	2.8
120	117.5	1.1

PATIENT IDENTIFICATION: 27 SEX: M AGE: 24

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: MANIC

TREATMENT: NEUROLEPTICS

TABLE LXXXV

PETTERSEN RATING SCALE FOR MANIA

ITEM	SCORE RANGE	ILLNESS SCORE	WELL SCORE
1. MOTOR ACTIVITY	1 - 5	2	1
2. PRESSURE OF SPEECH	1 - 5	2	1
3. FLIGHT OF IDEAS	1 - 5	2	1
4. NOISINESS	1 - 5	2	1
5. AGGRESSIVENESS	1 - 5	1	1
6. ORIENTATION	1 - 3	1	1
7. ELEVATED MOOD	1 - 5	2	1
8. GLOBAL RATING OF MANIA	1 - 5	2	1
	TOTAL	14	8

PATIENT IDENTIFICATION: 27 SEX: M AGE: 24

DIAGNOSIS: PRIMARY AFFECTIVE DISORDER - BIPOLAR

PHASE: MANIC

TREATMENT: NEUROLEPTICS

TABLE LXXXVI

SERUM PROLACTIN VALUES IN ng/ml.
L-DIHYDROXYPHENYLALANINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	15.1	10.5
20	12.7	5.8
40	13.2	5.6
60	8.6	1.2
90	15.6	4.2

TABLE LXXXVII

CHLORPROMAZINE CHALLENGE

TIME IN MINUTES	"ILL" VALUES	"WELL" VALUES
0	12.2	14.8
20	17.4	7.3
40	16.3	
60	19.2	13.8
90	16.7	17.1
120	20.2	16.2

5.2 STATISTICAL ANALYSIS

A considerable amount of variability in the Raw Data is evident. Reference to Table LXXXVIII (Summary of Statistics), and in particular columns "Standard Deviation" and "Coefficient of Variation", is indicative of this relatively high variability of the data at hand.

While on occasions experimental error may account for some of the variability, the accuracy of the assay technique, as indicated previously, is high. Due to the variability of the data, it was decided to apply non-parametric statistical procedures to the data, in an attempt to see whether or not there was a significant movement of prolactin values from the illness phases to the recovery phases.

The Wilcoxon Matched Pairs Signed Ranks Test was applied, not only to see the direction of movement but also to assess the relative magnitude of the shifts. The direction of movement is given by the sign of ill minus recovered scores. The significance of the magnitude of the ill minus recovered scores is given by the p = value.

Individual analyses were carried out for each of the values of prolactin at 0, 20, 40, 60, 90 minutes and at 120 minutes for the chlorpromazine challenge. Analyses were also carried out on the sum of the prolactin levels for each challenge procedure including the baseline values, i.e. the sum of values from time 0 to 90 minutes for L-dihydroxyphenylalanine, and to 120 minutes for chlorpromazine.

The results of the analyses of each of the challenge procedures (1) depressives/L-dihydroxyphenylalanine, (2) depressives/chlorpromazine, (3) manic/L-dihydroxyphenylalanine, (4) manic-chlorpromazine are presented in Tables LXXXIX - XCII with appropriate comments.

Summary of Statistics

TABLE LXXXVIII

VARIABLE	NUMBER OF PATIENTS	MEAN	STANDARD DEVIATION	MINIMUM VALUE	MAXIMUM VALUE	COEFFICIENT OF VARIATION
DPB1	21	6.914	4.967	0.0	18.100	0.71838
DPC1	21	3.814	3.238	0.0	10.800	0.84882
DPD1	20	3.330	3.230	0.0	9.600	0.97001
DPE1	21	3.776	3.717	0.0	13.500	0.98420
DPF1	21	3.586	3.534	0.0	12.000	0.98562
CB1	21	6.519	5.051	0.0	17.600	0.77488
CC1	21	6.662	4.517	0.0	15.100	0.67807
CD1	21	8.386	5.044	0.0	19.100	0.60149
CE1	20	11.729	6.815	0.0	23.500	0.58107
CF1	19	13.445	7.641	0.0	26.300	0.56930
CG1	21	13.853	6.073	0.300	26.800	0.43843
DPB2	21	9.762	11.484	0.0	49.800	1.17643
DPC2	21	5.290	6.202	0.0	25.300	1.17234
DPD2	20	4.767	7.624	0.0	33.200	1.59954
DPE2	21	4.750	7.228	0.0	30.700	1.52170
DPF2	21	5.267	8.922	0.0	41.500	1.69396
CB2	21	10.852	8.341	1.400	34.000	0.76854
CC2	21	9.114	7.223	2.100	32.900	0.79251
CD2	20	13.114	9.647	1.500	42.000	0.73558
CE2	18	17.700	12.877	3.400	62.300	0.72752
CF2	19	21.494	14.540	5.300	68.800	0.67647
CG2	19	21.984	14.636	7.200	69.300	0.66576
DPB3	8	17.875	11.832	3.100	38.800	0.66192
DPC3	8	8.275	5.258	2.500	15.200	0.63536
DPD3	8	6.850	5.414	0.0	13.800	0.79040
DPE3	8	5.337	4.334	0.0	10.800	0.81203
DPF3	8	6.337	4.257	0.0	15.600	0.67167
CB3	8	16.637	10.132	2.000	32.500	0.60895
CC3	8	22.650	16.991	3.600	52.900	0.74974
CD3	8	35.450	33.731	4.400	90.600	0.95151
CE3	8	48.612	45.783	5.000	120.800	0.94180
CF3	7	56.637	59.700	7.000	151.200	1.05406
CG3	8	61.929	55.673	7.000	126.000	0.89898
DPB4	8	6.887	3.030	1.300	10.500	0.43994
DPC4	8	2.675	2.170	0.0	5.800	0.81113
DPD4	8	2.912	1.809	0.300	5.600	0.62113
DPE4	8	2.862	1.859	0.0	5.800	0.69804
DPF4	8	2.875	1.840	0.0	5.900	0.63994
CB4	8	7.175	4.090	2.000	14.800	0.57003
CC4	7	7.212	3.429	1.200	13.500	0.47537
CD4	8	8.814	6.654	1.200	20.500	0.75490
CE4	7	16.300	15.852	0.600	53.400	0.97253
CF4	7	23.329	26.555	2.800	81.600	1.13830
CG4	7	23.857	15.058	1.100	51.300	0.63117

5.2.1 Depressives : L-dihydroxyphenylalanine Challenge Data Analyses

Table LXXXIX gives the results of the statistical analysis of prolactin values resulting from investigations during the depressive phase and on recovery following L-dihydroxyphenylalanine challenge, including baseline values. It can be seen that all shifts were in a negative direction (sign of ill minus recovered), that is the values of prolactin levels moved from lower to higher levels on recovery. These changes in values were not statistically significant. Value C (being at time 20 minutes) shows the most significant change ($p = 0,0582$). An analysis of the sum of the individual values (sum of times) failed to attain significance ($p = 0,1842$).

TABLE LXXXIX

Phase of Illness	Challenge	Time in Minutes	Sign of Illness Minus Recovery	p-value
Depressed	L-dihydroxy-phenylalanine	B-0	-	0,2736
		C-20	-	0,0582
		D-40	-	0,4997
		E-60	-	0,3812
		F-90	-	0,4080
		Sum of times	-	0,1842

5.2.2 Depressives : Chlorpromazine Challenge Data Analysis

Table XC gives the results of the statistical analysis carried out on prolactin values resulting from investigation during the depressive phase and on recovery with chlorpromazine challenge. Again both the individual values at the different times and the sum of the individual values were subjected to analysis.

It can be seen that a number of significant results were obtained. A significant change was found on the sum of the

individual values p = 0,0058, as was the case with the baseline measures B (p = 0,0096) and the measures at times, D (p = 0,0157), E (p = 0,0038), F (p = 0,0065), and G (p = 0,0168). The value of C being the least significant (p = 0,0680).

TABLE XC

Phase of Illness	Challenge	Time in Minutes	Sign of Illness Minus Recovery	p-value
Depressed	Chlorproma-zine	B-0	-	0,0096
		C-20	-	0,0680
		D-40	-	0,0157
		E-60	-	0,0028
		F-90	-	0,0065
		G-120	-	0,0168
		Sum of times	-	0,0058

Not only were the changes significant but all were in the direction from lower values when depressed to higher values when recovered. There were, therefore, significant changes on the chlorpromazine challenge test times 0, 40, 60, 90 minutes and the sum of the individual values. It would appear, however, from this data that the challenge with chlorpromazine is probably unnecessary in that the baseline values would be a good index of the disturbance of prolactin regulation in the depressed phase, baseline change being highly significant (p = 0,0096). Very significant results here indicate that the prolactin levels are lower in the depressed phase and increase upon recovery from depression.

5.2.3 Manics : L-dihydroxyphenylalanine Challenge Data Analysis

Table XCI gives the results of the statistical analysis of prolactin values resulting from investigation during the manic phases and on recovery with the L-dihydroxyphenylalanine chal-

lenge procedure.

As occurred previously individual value changes at the various times and the changes in the sum of the values in the manic and recovery phases were analysed.

There was a significant change in the sum of the individual values from the manic phase to the recovery phase (p = 0,0050) the direction of these changes was from higher values to lower values upon recovery (ill minus recovery being positive).

Baseline levels B (time 0 minutes) also changed in the same direction and attained significance at the 0,0521 level.

Changes in values for prolactin at times C (20 minutes) and F (90 minutes) attained significance at the 0,0500 level. While other value shifts did not reach significance all the signs were positive indicating that the changes were in the direction of high when manic to lower levels of prolactin upon recovery.

TABLE XCI

Phase of Illness	Challenge	Time in Minutes	Sign of Illness Minus Recovery	p-value
Manic	L-dihydroxy-phenylalanine	B-0	+	0,0251
		C-20	+	0,0500
		D-40	+	0,1235
		E-60	+	0,2626
		F-90	+	0,0500
		Sum of times	+	0,0500

5.2.4. Manics : Chlorpromazine Challenge Data Analyses

Table XCII gives the results of the statistical analysis on prolactin values resulting from investigation during the

manic phase and on recovery with the chlorpromazine challenge procedures.

The shift in values of prolactin were positive at times 0, 20, 40, 60, 90 and 120 minutes. This indicated a decrease from higher levels to lower levels on recovery. The change of values obtained at times, C (20 minutes), D (40 minutes) and E (60 minutes) were significant at 0,0173, 0,028 and 0,0173 respectively. The change in value for the sum of the values at the different times failed to attain significance (p = 0,0679). The direction of change was again positive indicating a shift from higher levels to lower levels on recovery.

TABLE XCII

Phase of Illness	Challenge	Time in Minutes	Sign of Illness Minus Recovery	p-value
Manic	Chlorproma-zine	B-0	+	0,1235
		C-20	+	0,0173
		D-40	+	0,0280
		E-60	+	0,0173
		F-90	+	0,8658
		G-120	+	0,2489
		Sum of times	+	0,0679

5.2.5 Motor Activity and Prolactin

Of particular interest is the relationship between motor activity and changes in prolactin from ill to recovered. The depressive scale item "retardation" was considered to be indicative of "impaired" motor function. This item is fairly heavily weighted having a five point rating. In the manic group the level of motor activity is given on the "motor activity" scale; this also having a five point rating.

The results of the analyses of variance are not given as

problems were experienced in handling the data. When looking at the various ratings for both retardation and motor activity the number of subjects in the various groups of retardation/motor activity proved to be small. The largest group obtained for any rating was in the "variable one" group (depressed : L-dihydroxyphenylalanine) with ratings of three on retardation (n = 5). No really useful information was derived from these analyses. An increase in the number of subjects is very desirable in order to obtain significant information. This should be considered for a follow-up study.

CHAPTER 6

DISCUSSION AND CONCLUSIONS

6.1 DISCUSSION

6.1.1 Depressive Subjects' Data Analyses

Discrepancies in the results of the statistical analyses as seen in Tables LXXXIX and XC require consideration:-

The L-dihydroxyphenylalanine challenge was the first challenge to be done on each subject. It is possible that the novelty of the situation, as this was the first contact with the research procedure, increased the stress in these subjects. It is also possible that the stress effect was not short lived but was relatively sustained throughout the 100 minute period of investigation.

The depressed subjects, as these were on the first encounter, are more likely to respond with excessive stress than recovered subjects, particularly as the recovered groups were no longer naive.

Both these effects could raise the levels of prolactin. Such a possible rise in the depressed period could reduce the magnitude of the change in prolactin values, thus leading to a reduction of the significance of the changes. One may have expected the baseline (time 0) values to have been substantially affected. The changes in values are in the same direction (sign of ill minus recovered is negative) i.e. low values in the depressed phase to higher values on recovery.

In view of the fact that the L-dihydroxyphenylalanine challenge was generally carried out on the day before (24 hours) the chlorpromazine challenge, the emergence of positive results on the chlorpromazine challenge may have been influenced by some "priming effect" by L-dihydroxyphenylalanine. It is,

however, to be noted that the same procedure was carried out with the recovery challenge, making the effects in all probability, comparable. It is still possible that in the condition of depressed or recovered there may be a greater susceptibility to "priming". In the unlikely event of such an effect it is improbable that the validity of the test would be affected.

6.1.2 Manic Subjects' Data Analyses

The discrepancies here are not so problematic. On the whole significant results were obtained from both the L-dihydroxyphenylalanine and the chlorpromazine challenges. Unfortunately the baseline values (time 0 minutes) for the chlorpromazine challenge failed to reach significance ($p = 0,1235$), nor did the sum of the individual values show a significant shift ($p = 0,0679$).

A number of factors operated here which probably reduced the significance of the changes in values. The sample of subjects ($n = 8$) is rather small. In view of the clinical difficulty of handling these patients while observing a washout period, only hypomanic and moderately manic patients can be operationally managed. A further factor was that older patients were included (one of 79 years) who should probably not have been admitted to the study. It is evident from looking at the raw data that these patients did not conform to the pattern of the younger patients. This may well be a product of the ageing process. Further studies are required to clarify this matter. The difficulty of obtaining suitable hypomanic/moderately manic patients lead to the inclusion of these elderly subjects who were easier to handle. This may be a significant selecting factor as age may well be associated with some muting of the amplitude of the disturbance of prolactin activity.

6.1.3 Significance of Results

This study has produced substantial evidence that dopamine function may be disturbed in primary affective disorders.

It may be argued that there is a non-specific disturbance in prolactin function and not primarily a dopamine dysfunction. Such a non-specific disturbance being possibly stress related, should lead to increased levels of prolactin in the depressive phase, making this explanation unlikely.

A further possibility is that other transmitter regulating factors may be disturbed, explaining the apparent inversion of expected or hypothesised prolactin levels in depression and mania. Serotonergic stimulation of prolactin is via the prolactin releasing factor. Reduced serotonergic function, for instance, would lead to reduced levels of prolactin - in keeping with the traditional indoleamine theory of depression. This may indeed be so, but there is reason to believe that over and above any such influence dopamine is also subject to disturbance.

Another non-specific disturbance, at pituitary level, can be postulated, this could explain the depressive effects as being due to a generally "sluggish" pituitary. Manic effects would be more difficult to explain on this basis, as would be the disturbance seen in the pituitary adreno-cortical axis.

The non-specific effect of "motor behaviour" should be approached with extreme caution. What constitutes a non-specific effect and what is indeed a highly specific effect is of fundamental importance, as dopamine is probably the primary transmitter in driving and executing motor function!

The expectation that a hyperdopaminergic state occurs in mania and a correspondingly hypodopaminergic state occurs in depression, would not readily explain the reverse effects seen in the prolactin values in this study. The expectation would

be to find reduced levels of prolactin in mania, increased dopamine function giving rise to increased inhibition of prolactin. Depression conversely may be expected to be associated with raised prolactin levels due to reduced inhibition by dopamine.

The apparent difficulty in relating the prolactin changes to dopamine function may be purely due to the fact that the relationships within the dopamine systems are disturbed. An apparent balance exists between the inhibitory and the excitatory systems (van Rooyen 1980). The implication is of a reciprocal relationship with both inhibitory and excitatory functions available, the emergence of a reverse pattern could be expected.

The dysfunction of inhibition may be an expression of increased excitatory (D_2) system function in mania, excitatory ascendency with a relative reduction of inhibition. In depression the impaired excitation may then be associated with a relative increase of inhibition, hence the lower levels of prolactin.

The mechanisms of such a change is unclear, whether the D_2 system drives neurones which inhibit the tubero-infundibular neurones remains to be elucidated; possibly neurones of the incertohypothalmic system. Opposing effects of D_1 and D_2 dopamine receptors on adenylate cyclase has been referred to previously (Stoof and Kebabian, 1981). Conversely disturbance within the inhibiting systems may give rise to increased excitatory function due to lack of modulation by the D_1 system in mania. The reverse would hold for depression.

Some disturbance of the dopamine receptors (D_4) is suggested by supersensitivity patterns which certainly indicate modified receptors. These changes are more likely to be secondary than primary.

Examination of the raw data on pages 119,121, 123, 131 and 133 suggests that not only is there a reduced inhibitory

function in mania, but that the dopamine receptors may be supersensitive. As stated before, the data may be distorted by the very elderly patients (79 years), while many of the other patients show a clear trend to a supersensitivity pattern. The raw prolactin data of patients, identification numbers 2, 9 and 26 in particular, demonstrate high receptor sensitivity (see pages 119, 121 and 131 respectively). Examination of the raw data on pages 91 and 121 show the depressive and manic data of the same patient. This data shows gross shifts in prolactin levels from depressed to manic state. Again the receptor supersensitivity pattern is evident (page 121). The problem of the nature of the dopamine receptors on the pituitary mammotrophs is most important. They appear to be inhibitory either non-adenylate cyclase dependent, or negatively regulating adenylate cyclase. An additional factor is the high level of sensitivity of these receptors (see discussion on dopamine receptors). They may not be identical to those occurring elsewhere despite significant similarities to the D_2 receptors. It may be difficult to extrapolate from data derived from their functional changes.

Additional factors in discussing the results of this investigation need to be emphasised. While the D_4 dopamine receptors appear to be important on the mammotrophs, D_1 receptors have also been demonstrated in the adenohypothesis (van Rooyen 1980). Reduced dopamine inhibition (D_1) could lead to release of dopamine excitation (D_2) due to their oppositional relationship (Stoöf and Kebabian, 1981). Further knowledge of this relationship will be helpful in throwing light on the changes seen in the present study.

A recent study by Cookson et al, (1983) showed changes in prolactin levels in manic patients in response to intravenous haloperidol. There was also a trend to higher than normal levels of prolactin. This latter finding may relate to the results of this study, although Cookson's study was conducted under very different circumstances.

Involvement of the endorphins in modulating dopamine function

may explain the changes in prolactin levels demonstrated by this study. Beta-endorphin exerts an inhibitory effect on dopaminergic inhibition (Fuxe et al, 1980). Should the levels of endorphin be low in depression inhibition of dopaminergic inhibition would be reduced, i.e. dopaminergic inhibition would increase and prolactin levels would fall. The converse would hold for mania producing a rise of prolactin. Changes in mood and the experience of pain associated with the various phases of bipolar illness may also be explained.

D-ala-enkephalin, beta-endorphin and analogues have been shown to have opiate-like effects when administered centrally. Behavioural activation occurs at low doses and analgesia. High doses are associated with euphoria and sedation. Of great interest is the fact that behavioural activation is associated with peptide action on the mesolimbic dopaminergic system (Koob et al, 1984).

This interface between the peptides and the monoamine systems requires further investigation. The reduction of experience of pain seen clinically in mania and possibly the increased sensitivity to pain in depression, may be associated with changes in the peptide systems. Effects on mood are perhaps even more obvious. The present study has drawn on this relationship quite unexpectedly.

6.1.4 Prolactin in Mania

While we can speculate on what the causes of the changes in prolactin levels may be, the actual changes demonstrated were borne of theoretical consideration on dopamine function in primary affective disorders.

This study has demonstrated shifts in prolactin levels from depressed (lower) to recovered, and from manic (higher) to recovered, the patients having been used as their own controls. The fact that no "normal" controls were used is a drawback to this study.

The normal values as determined for the particular assay used are quoted as extending to 13ng/ml (Rianen Assay System). A 97,5 percentile cut-off was used, having conducted their study on 72 "normal" subjects. Frantz (1978) quotes the upper reference as being 20ng/ml for males and 25ng/ml for females in his study.

It is highly probable that a number of the manic subjects in this study exceeded the upper limits of normal, on baseline prolactin measures while in the manic phase. Reference to patients identification numbers, 2, 9, 19, 26 and 27 on pages 119, 121, 127, 131 and 133 respectively, are cases in point. These refer to five manic patients all of whom had baseline prolactin levels beyond 13ng/ml. This holds for all five subjects whether the maximum baseline values or the means of baseline values are accepted. This would appear to be appropriate as the "upper normal" for this assay technique is quoted as 13ng/ml. Patient identification number 25 (page 117) was virtually 80 years old when studied and as can be seen his prolactin values are entirely out of keeping with the other manic patients. It would appear to be legitimate to discard this patients' data. Under these circumstances five of the total of seven manic patients may have elevated levels of prolactin. This is approximately 70% of the sample. Taking the cut-off point as 25ng/ml three of the seven subjects' prolactin levels extend beyond 25ng/ml, that is about 40%.

The sample is obviously small and caution must be observed in drawing conclusions. Taken in conjunction with the previous analyses which suggest that there are indeed statistically significant shifts in prolactin levels from manic to recovered in a downward direction, the above discussion can only be supported. On this small sample of seven patients suggestive evidence of elevated prolactin levels in the conservative region of 50% of manic patients can be expected.

6.1.5 Future Development

Rating scales of a more comprehensive type should be sought.

The narrow view reflected in the Hamilton Depressive and Pettersen Scales are problematic. They do not adequately allow behaviour to be viewed across the entire range of its possibilities.

A further problem is the heavy loadings placed in areas which do not appear to be fundamental. For instance, the last three items of the Hamilton Scale are loaded to a maximum but probably all three reflect secondary cognitive effects.

Further work needs to be done in affective disorders. Adequate numbers of subjects to allow breakdown into bipolar and unipolar types will be most interesting. It is likely that the bipolar group will show more profound disturbance of dopamine function than will the unipolar group.

Mania is likely to be particularly rewarding despite the operational difficulties of managing these patients. Exclusion from the study of patients over 65 years of age appears to be warranted in both the depressed and manic groups.

Full challenge procedures appear to be necessary as these give considerably more information than do baseline measures alone. The possible receptor supersensitivity revealed bears witness to this fact.

Investigation during sleep may also prove to be productive, following claims that disturbance of prolactin is greater in sleeping than in waking depressive subjects (Halbreich et al, 1979).

More extensive profiles of biological data in the manic, normal and depressed phases are certainly desirable. It is preferable not only to study the various phases but also to incorporate a "normal" control group of subjects. This constitutes a very demanding research project, possibly a smaller number of patients intensively investigated in the different phases of the illness will be useful.

It is highly desirable that biological disturbances be defined in these disorders, such that organically measurable markers be available for diagnostic, classificatory and possibly treatment purposes.

Investigation of motor activity and prolactin level changes from ill to recovered, or possibly manic to depressed, should be conducted with adequate numbers of subjects. It may then be possible to establish a causal relationship between dopamine function and motor activity on the one hand, and prolactin on the other. The relationship between prolactin and motor activity thus being causally linked via dopamine.

Attention should be given to the peptide molecules and the role of the opiate receptors. Research strategies are under consideration in this regard.

6.2 CONCLUSION

A number of positive findings have emerged from this study. The implications of these findings remain to be clarified. The main findings are as follows:-

A significant change in prolactin levels from illness to recovery phases has been demonstrated in primary affective disorders. The depressive phase is associated with lower levels of prolactin. This is not an absolute lowering but is relative to the patients "well" state. Manic patients have an increase of prolactin levels, which appear to be absolute in over 50% of the subjects.

A number of manic subjects appear to have dopamine receptor (D_4) supersensitivity. A full pharmacological challenge procedure is necessary to demonstrate this effect.

The possible causes of these changes are discussed, with an emphasis on the role of dopamine, and a brief view of possible future studies is given. Mania remains a particularly fruitful area for research, but it remains operationally a difficult

condition to study.

The relationship of prolactin levels to motor activity is an important one, in view of the probability that dopamine regulates both motor activity and prolactin. Motor activity may be profoundly disturbed in primary affective disorders. Covariance of prolactin levels and ratings of motor activity could not be demonstrated, largely as a result of sample sizes. This defect could be corrected by extending the present study to obtain adequate sample sizes, so that analysis is feasible. More complex approaches or strategies may be required to demonstrate a specific relationship between prolactin and motor activity.

The present study has demonstrated a reversed pattern of prolactin secretion from that which was hypothesised, indicating a possible decrease of dopamine inhibition in mania and an increase of inhibition in depression. Controversy still surrounds the characterisation of dopamine receptors. Indications of supersensitivity of dopamine receptors in mania suggests that disturbance of dopamine is involved in the dysregulation of prolactin. The changes in the receptors are probably secondary, as this explains the data better than primary changes in the dopamine receptors.

The responses of prolactin to challenges in the depressed phase need to be evaluated against normal controls in order to assess the degree of blunting of these responses.

Possible mechanism underlying the changes demonstrated are discussed. Future studies should attempt to use the patients as their own controls and include "normal" controls.

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PERSONAL COMMUNICATIONS - UNPUBLISHED DATA

Hart GAD. Sulpiride in the treatment of mania: A pilot study. 1982

CHEMICAL SUPPLIES AND LABORATORY EQUIPMENT

Rianen Assay System Prolactin (^{125}1) Radioimmunoassay Kit. Cat.No. NEA -095.