THE DST AND PSYCHIATRY:
POSSIBLE EFFECTS ON DECISION MAKING, DIAGNOSIS AND TREATMENT

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in fulfilment of the requirement for the degree of
Master of Clinical Science

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December 1983.

TABLE OF CONTENTS: Page

TABLE OF CONTENTS (continued)

SUMMARY:

The introduction of a technique that purports to increase our understanding of a particular disorder leads inevitably to a reassessment of the existing body of knowledge about that disorder. Sometimes a re-evaluation of the methods of the discipline may occur.

When one such innovation, the dexamethasone suppression test (DST), was introduced into clinical psychiatry at the Royal Adelaide Hospital, a study was conducted into its effects on diagnosis and treatment of depression. The results of this study, which are detailed in Chapter Three of this dissertation, indicate that considerable changes in management (and also perhaps in thinking about clinical problems) occurred concurrently with the introduction of the DST. Specifically, the study showed increases in the diagnosis of biological depression and treatment with antidepressants. There was no association between DST results and particular management plans. There was, however, a very strong association between requesting the DST and subsequent management with antidepressants.

These results led to a re-evaluation of the literature of the development of the DST as a specific laboratory test for melancholia. Chapter Two follows Rubin and Mandell's hypothesis that elevated cortisol levels were a specific concomitant of depression, through nearly 20 years of research. In particular, the rapid increase in the literature on the DST in the early '80s is reviewed.

SUMMARY (continued)

The chapter ends with a discussion of some very recent cautionary articles about the application of the DST to psychiatry.

The results of the DST study led also to a re-evaluation of one of the fundamental processes of psychiatry and of all medicine, the process of clinical judgment. Chapter One is concerned with decision making in psychiatry and how the process in psychiatry differs from that in general medicine. Issues of diagnosis are considered, along with the relevance of diagnosis to treatment. The notion of a psychiatrist's "set" with respect to management is commented upon, along with the notion of maximising utility with respect to diagnosis and treatment.

The dissertation concludes with only conjectures to explain the results. Studies to address these conjectures could lead to a greater understanding, not only of the DST, but also to the process of clinical judgment in psychiatry.

CERTIFICATION:

This thesis contains no material which has been accepted for the award of any degree or diploma in any university and, to the best of my belief, contains no material previously published or written by another person, except where due reference is made in the text.

Signed:

Geoffrey David Schrader

ACKNOWLEDGMENTS:

I would like to thank Dr T.C. Durbridge and Ms D. Hill, who greatly assisted with the study; Professor I. Pilowsky who provided many helpful comments; Professor J. Darroch who gave much assistance with the statistical analysis of the data; and my wife, Sue.

CHAPTER ONE:

DECISION MAKING, DIAGNOSIS AND TREATMENT IN PSYCHIATRY:

1. Decision Making in General Medicine.

The rapid increase of information concerning the nature of anatomical, physiological and biochemical abnormalities occurring in particular diseases has led inevitably to the development of the study of the methodologies by which physicians decide whether a disease is present and how it is best treated. Even with the large amounts of information about their patients' anatomy, physiology and biochemistry which physicians may have at their disposal, decisions about diagnosis and treatment are still decisions which entail the balancing of probabilities, the exercising of clinical judgment. Clinical judgment is often regarded as the "art" of medicine, the process by which the experience of similar previous cases is combined with the current clinical presentation and a diagnosis and a management plan distilled from the mixture.

There have been several attempts to explore rationally the logic of this "intuitive" aspect of medicine. One of the most widely studied theories for making decisions under conditions of uncertainty, and one which has been said to closely approximate the process of the diagnostic process, is Bayes' theorem[1]. This theorem was devised by the Rev. Thomas Bayes, an 18th century English clergyman. It provides a method to quantify the

means by which new evidence is used to modify prior judgments.

Lusted[2] has applied Baysian probability theory to medicine in general, and to diagnostic radiology in particular. However, wider applications of this attempt to formalise and improve medical decision making have been slow in arriving. An editorial[3] of the New England Journal of Medicine in 1975 commented that this lack of application of decision theory to medicine may reflect a difficulty many physicians have with the mathematics any attempt to systematise clinical judgment entails. It added the caveat that any decision making theory can only provide decisions of similar validity to the data supplied.

So if, overall, the application of systematised decision making theory to medicine has been slow, what of its particular relevance to psychiatry? Before an answer to this question can be attempted, it is necessary to consider the nature of diagnosis in psychiatry.

2. Psychiatric Diagnosis.

The problems of diagnosis in psychiatry are numerous. It has been argued by Szasz[4] that psychiatric disorders are not diseases but expressions of "problems in living", and therefore the process of medical diagnosis is inappropriate when classifying these problems. Rosenhan[5] has argued that "unlike most medical diagnoses, which can be validated in various ways, psychiatric diagnoses are

courses. For example, individual ailments such as a pain in the knee, a pain in the big toe and a tophus in the ear, could be classified as a cluster of ailments commonly occurring together - the disease gout. In psychiatry, the description of behaviour and the recording of the experiences of patients has enabled an impressive amount of data to be amassed. Observations of Kraepelin, Jaspers and Fish have culminated with the development of instruments such as the Present State Examination[7] for the classification of psychiatric symptoms.

However, there needs to be general agreement on just what cluster of symptoms constitutes which particular syndrome or disorder. This agreement on what constitutes a particular disorder is most important for accurate communication. That wide disagreements have occurred about what constitutes a particular disorder, was clearly demonstrated by the US - UK[8] diagnostic project. In this study, it was discovered, the greater number of patients diagnosed as having schizophrenia in the US, as compared with the UK, was not due to a different incidence of schizophrenia, but rather to a broader concept of schizophrenia used by American psychiatrists. American psychiatrists tended to find higher levels of psychopathology in all areas; they also had a much broader concept of thought disorder. It thus appeared that, as well as significant criterion variance for diagnosis, there was also considerable observation and interpretation variance

between American and English psychiatrists. On the other hand, results of the International Pilot Study of Schizophrenia[9] tended to suggest that, in general, apart from psychiatrists in Moscow and Washington, similar concepts of schizophrenia were held by psychiatrists in developed and underdeveloped countries throughout the world.

Given the state of the knowledge of psychiatric disorders in the late '70s and the problems associated with psychiatric diagnosis, the American Psychiatric Association produced its third Diagnostic and Statistical Manual[10] - DSM III - in 1980. The DSM III provides explicit criteria and decision rules for the diagnosis of psychiatric disorders. The criteria are, in general, descriptive apart from the few disorders where aetiology or pathophysiological processes are known. The aetiology of psychiatric disorders is to a large extent ignored by the DSM III classificatory system. As such, the DSM III is open to the criticism of too early closure. Bronowski[11] has said: "A science which orders its thought too early is stifled". However, the DSM III classificatory system has met with acclaim from Feinstein, an authority on clinical judgment. Feinstein[12] says of the inclusion of explicit diagnostic criteria in the DSM III:

DECISION MAKING, DIAGNOSIS AND TREATMENT IN PSYCHIATRY

> "The production of operational identifications has been a pioneering unique advance in nosology ..... In the field of diagnostic nosology, the establishment of operational criteria represents a breakthrough that is as obvious, necessary, fundamental and important as the corresponding breakthrough in obstetrics and surgery when Semmelweiss, Oliver Wendall Holmes and, later on, Lord Lister demanded that obstetricians and surgeons wash their hands before operating on the human body ..... The absence of such criteria is what has made the rest of the ICD (International Classification of Diseases) such a shambles, because of the inconsistent way in which the nomenclature is applied".

The DSM III system, then, is an attempt to define the "what is it?" problem of psychiatric diagnosis; it makes no attempt to address the question "how has 'it' occurred?"

In general medicine, even though clusters of symptoms could be recognised as diseases such as gout, with a predictable natural history, the aetiology of such diseases, the "how" question was only answered when autopsy studies and laboratory technology, along with animal experimentation, were developed. This is not to say the "how" question was not addressed in general medicine prior to the development of morbid anatomy and laboratory technology. The desire to understand observed phenomena in terms of a general explanatory theory is, of course, not new. It is merely that prior to these developments aetiological theories in medicine did not, in general, have much utility with respect to treatment.

DECISION MAKING, DIAGNOSIS AND TREATMENT IN PSYCHIATRY

Similar attempts to explain observed phenomena occurring in psychiatric disorders in terms of aetiology have, of course, occurred. Freud's diagnostic classification was based primarily on aetiology and not on symptomatology, viz., the traumatic neuroses, the actual neuroses and the psychoneuroses. Freud's attempt to arrive at a diagnostic system was flawed, according to Brenner[13], in not deriving from adequate data. He takes as example two of Freud's diagnoses: neurasthenia and anxiety neuroses. These syndromes had different dynamics and different aetiologies.

> "Excessive masturbation or nocturnal emissions comprised the first group of pathogenic, sexual abnormalities. They produce symptoms of fatigue, listlessness, flatulence, constipation, headache and dyspepsia. Freud proposed that the term neurasthenia be henceforth limited to this group alone. The second type of sexual noxia was any sexual activity which produced a state of sexual excitement or stimulation with an adequate outlet or discharge, as, for example, coitus interruptus or love making without sexual gratification. Such activities resulted in states of anxiety, most typically in the form of anxiety attacks, and Freud proposed that such patients be diagnosed as anxiety neurosis".

In a discussion of psychoanalytic diagnosis, Stoller[14] has commented that psychoanalytic thinking has often confused the distinction between "concomitant with" and "aetiological for".

Biological aetiological theories have been successful in providing an understanding of the neuropathology and

successful treatment of some psychiatric disorders. Most notable are probably the discovery of the association between central nervous system infection by Treponema pallidum and a general paralysis of the insane, and the association between niacin deficiencies and psychosis. Feinstein[12] has commented on the impact of similar such aetiological discoveries in general medicine. Wherever what Claude Bernard has called a "proximal cause" for a disease was identified, there was a change in the name of the disease. The old clinical entity of dyspnoea, for example, became the pathological entity pneumonia. Later, when its aetiology was further understood, it became staphylococcal pneumonia.

However, generally the process of being able to classify most psychiatric disorders on the basis of a biochemical or physiological aetiology has not been possible, as it has been in general medicine. The search for any pathology or disturbed physiology in the major functional psychoses and the neuroses did not, till very recently, prove fruitful. However, some "markers" of disturbed brain function specific for certain psychiatric diagnosis - for example, a positive dexamethasone suppression test in endogenous depression[15] - have been discovered. Such biological markers would appear to have no particular immediate relevance to aetiology. They do, however, add to the validity of diagnostic categories such as endogenous depression.

In summary, it appears that the process of diagnosis is generally applicable to the study of psychiatric disorders. The history of the classification of diseases in general medicine is similar to the history of such classifications in psychiatry. It does appear possible to establish diagnostic criteria for psychiatric disorders. These disorders do follow a generally predictable natural history. An aetiological underpinning of psychiatric diagnosis is less well established than in general medicine. With a few exceptions, aetiological explanations for particular diagnostic categories are not available.

3. The Process of Diagnosing in Psychiatry.

Let us now consider in more detail the process of arriving at a diagnosis in psychiatry. Nurcombe[16] has considered the process to be similar to diagnosis in general medicine. According to Nurcombe and Fitzhenry-Coor:

> "From a cognitive standpoint, medical problem solving appears to be a set of operations involving memory organisation, decision-making and probability estimation .....
>
> The cognitive strategies are as follows: (to) elicit, recognise and evaluate salient cues; (to) assemble cue-clusters in such a way as to delineate a clinical problem; (to) develop a structured array of diagnostic hypotheses; (to) develop an enquiry strategy derived from the array of hypotheses; (to) weigh positive and negative evidence; (to) formulate a comprehensive and an individualised plan of management".

They have produced evidence from a study of clinical reasoning during psychiatric interviews, that experienced psychiatrists produce more hypotheses earlier in the interview than less experienced residents. They have also shown that, with experience, clinicians became more explicit in their explanations for particular decisions. They also found that the more experienced clinicians were more able to continuously re-evaluate early hypotheses in the light of new information. There would seem, then, to be no major differences in the logic of this schema for diagnosis and that which Feinstein has described as occurring in general medicine. Additional rules of particular importance in clinical reasoning in psychiatry are, according to Nurcombe and Fitzhenry-Coor, the toleration of uncertainty and the avoidance of premature closure on one possibility, the distinction between observation and inference, awareness of personal reactions to particular patients and the distinction between accurate empathic identification and the projection of personal conflicts onto patients.

However, Lazare[17] has suggested other factors may be of importance in decision making in psychiatry. Lazare describes four conceptual models used by psychiatrists - medical, psychological, behavioural and social. He suggests that different courses of management arise from each model, and that the psychiatrist's choice of which model to use in his thinking about a particular patient

is determined by several factors. These include not only the diagnosis applied to the patient (this may have, of course, already been affected by a particular set held by the psychiatrist), but also the effectiveness of available treatments, the immediacy of the situation, the social class of the patient and, lastly, the "ideology" of the psychiatrist. Lazare refers to Armor and Klerman[18] who point out that "different ideological factions are most likely to occur when a codified knowledge base is markedly incomplete or ambiguous about the means to be used to attain a professional goal". Lazare feels that this is the current state in psychiatry. Ideologies in psychiatry give sway generally in the face of mounting evidence supporting a particular treatment. For example, the use of psychotherapy as a specific treatment of manic depressive illness has waned with the introduction of specifically effective treatment, Lithium Carbonate. With respect to the importance of social class in determining the psychiatrist's decision making, Lazare refers to the work of Hollingshead and Redlich[19], where the importance of social class in the application of psychotherapy was demonstrated. He uses the example of the soldier who becomes psychotic at the battlefront as an instance where the immediacy of the situation is of importance in decision making.

Feinstein views diagnosis as not an end in itself, but rather as just part of the logical process of

deciding on a course of management for the patient. The assumption is, of course, that in general medicine the correspondence between diagnosis and a particular treatment is high. Is this the situation in psychiatry? (Feinstein has enlarged upon factors other than diagnosis which determine treatment decisions in general medicine, as the correspondence between diagnosis and treatment is often not high in general medicine.) From the preceding discussion it would not appear to be so. Kendell[20] has echoed this point:

> "The existence of a treatment like cobalamin for pernicious anaemia or chloroquine for malaria, which is specific for a single diagnostic category and almost invariably effective on members of that category ..... at present no such situation exists in psychiatry".

Williams[21] has divided decisions about management of patients with psychiatric disorders into three levels. The first is the decision to refer the patient to a psychiatrist; the second is the psychiatrist's decision whether to admit the patient to hospital and the third is the decision of which specific treatment to use. Williams finds little evidence for the psychiatric diagnosis being greatly important in any of these decisions.

Several studies have examined the relationship between diagnosis and management in psychiatry. Bannister et al.[22] examined psychiatric case notes looking for associations between particular diagnoses and treatments. They found, in general, that a particular treatment did not follow a particular diagnosis. They tentatively concluded that variables other than diagnosis were important in predicting the course of treatment. Sandifer[23] looked more closely at

why psychiatrists differ in their decisions regarding treatment. He examined the diagnostic and treatment decisions of six psychiatrists who had watched a series of filmed interviews with patients. The psychiatrists' "sets" with respect to various treatment options such as psychotherapy and somatic therapies had been determined by a questionnaire given previously. He found considerable difference in treatment plans. Differences over the use of phenothiazines seemed best related to differences over diagnoses, while differences over whether to use psychotherapy seemed to be associated with the psychiatrists' "set" towards psychotherapy. Mayou[24] similarly found wide variations in treatment plans when 43 experienced psychiatrists were asked how they would manage a typical psychiatric problem - a married woman presenting with agoraphobia and mild depressive symptoms. Particularly, differences were found with respect to types of further information required, type of treatment, number and frequency of treatment sessions and the use of other therapists. The lack of congruence between diagnosis and treatment may, in part, reflect the multi-factorial aetiology of psychiatric disorder. The DSM-III multi-axial diagnostic system recognises the importance of considering various facets of the patient's current condition when determining management plans.

To recapitulate, the process of diagnostic decision making has been considered. Similarities have been drawn between decision making in psychiatry and the process of diagnosis in general medicine. The importance of factors other than diagnosis in decision making in psychiatry has been raised, as has the lack of specific treatments for many psychiatric disorders.

DECISION MAKING, DIAGNOSIS AND TREATMENT IN PSYCHIATRY

Given the preceding discussion of the nature of diagnostic decision making and treatment in psychiatry, it will now be considered whether more formal methods of decision making theory can be applied to psychiatry. Before, the application of decision making models to general medicine will be briefly considered.

4. Bayes' Theorem.

Bayes' theorem of probability theory is, according to Edwards et al.,[25] a formally optimal rule about how opinions should be revised in the light of new information. Lusted[2] believes that the intuitive process of diagnosis and clinical decision making, as performed by experienced clinicians, approximates the Bayesian statistical process. He also feels that by making decision making more explicit, and perhaps directly applying Bayesian statistical methods, the accuracy of clinical decision making could be improved. The Bayesian statistical approach finds an immediate application in the interpretation of laboratory test results. Following Galen and Gambino,[26] Bayes' formula allows a calculation of the *a posteriori* probability of a disease θ_i given a positive laboratory test result R. The *a posteriori* probability is the predictive value of a positive test result. To calculate the *a posteriori* probability, the following data is required:

(1) An estimate of the prevalence of the disease θ_1 is required. $p(\theta_1)$ is the *a priori* probability of the disease in the population;

(2) An estimate of the prevalence of non disease or other disease states is required. $p(\theta_2)$ is then the *a priori* probability of non disease or other disease states in the community. θ_1 and θ_2 are mutually exclusive $p(\theta_1) + p(\theta_2) = 1$.

The predictive value of a positive test result R, $p(\theta_1/R)$ is given by Bayes' theorem:

$$p(\theta_1/R) = \frac{p(\theta_1)\, p(R/\theta_1)}{p(\theta_1)\, p(R/\theta_1) + p(\theta_2)\, p(R/\theta_2)}$$

Note: $p(R/\theta_1)$ is the probability of a positive test result R, given that the patient has disease θ_1. It represents the test <u>sensitivity</u>.

$p(R/\theta_2)$ is the probability of a positive test result R given the patient has other diseases or no disease θ_2. It is equal to <u>1 minus test specificity</u>.

DECISION MAKING, DIAGNOSIS AND TREATMENT IN PSYCHIATRY

The importance of the *a priori* probability of the disease (its prevalence) in the population in which a particular test is used, was forcibly stressed by Galen and Gambino. The predictive value, derived from Bayes' theorem, is the value which determines how accurately a test will predict the presence or absence of disease. The prevalence of the disease in the population under study profoundly affects the predictive value, far more so than common sense would suggest.

Galen and Gambino cite, as an example of the importance of the prevalence of the disease under consideration, the test for Phenyl ketonuria (PKU). In this case the test has very high specificity and very high sensitivity; however, as prevalence of the disease is so low, the predictive value of the test is only 50%. This means that half the abnormal test results occur in subjects without PKU. This is what occurred when PKU screening became mandatory for all newborns.

Galen and Gambino state that the variables of sensitivity, specificity and prevalence and predictive value apply not only to laboratory test results but also to questions in the clinical interview. This is not surprising when it is considered that the predictive value is derived from Bayes' theorem which, as has been said previously, can be viewed as a formally optimum rule for revising old opinions in the light of new information.

Galen and Gambino further illustrate the effect of prevalence with an interesting explanation of the results of Rosenhan's[5] pseudo-patient study. If the prevalence of sanity is low in a psychiatric hospital, less than 0.1%, even if a psychiatrist can diagnose sanity with 95% sensitivity and 95% specificity, the predictive value of a positive result is only 2%. A false positive rate of 98% is so poor that any attempt to discover a very few sane amongst a massive number of insane would be unrewarding.

5. Bayes' Theorem and Psychiatric Diagnosis.

The application of Bayes' theorem to decision making in psychiatry will now be considered further. Kraus[27] derived a prediction of suicidal risk by applying conditional probabilities for suicidal behaviour with respect to variables of age, sex and diagnosis to Bayes' formula. He derived his data from psychiatric hospital case notes. He was thus able to produce posterior probabilities for the risk of suicide; for example, in a woman, aged 40, with a diagnosis of reactive depression. Kraus also employed Bayesian statistics to derive the likelihood of a particular diagnosis, given the prevalence of the disorder and conditional probabilities for various symptoms. Kraus points out that by judicious adjustment of prior probabilities it is possible, using Bayes' theorem, to minimise undesirable decision errors.

Mellergard and Leroy[28] similarly derived conditional probabilities for the presence of certain variables including family history of mental illness, previous hospitalisation, previous treatment, specific symptoms, etc., in various psychiatric disorders. Using Bayesian statistics, they were able to give an indication of the value of a particular piece of data (for example, social history), for a particular diagnosis (for example, schizophrenia). They were also able to indicate which parts of the psychiatric interview were likely to be of most importance for the diagnosis of a particular psychiatric disorder.

In a further paper, Mellergard and Leroy[29] compared the diagnoses generated from conditional probabilities for symptoms using Bayes' theorem with actual clinical diagnostic decisions. They looked at the differential diagnosis between "endogenous depression", "neurotic depression" and "anxiety neurosis". They found that the clinician's diagnosis of endogenous depression occurred with greater frequency than was expected according to Bayes' theorem. That is, the diagnosis of endogenous depression was made more often than the information base indicated it should be made. Mellergard and Leroy relate this observation to the inclination of the clinician to give the patient a trial with antidepressants. The clinicians behaved as if the prior probability of endogenous depression was higher than it actually was. According to

Edwards[30] "people maximise the product of utility and subjective probability".

Pilowsky and Durbridge[31] have devised a Diagnostic Utility Index which is a method for eliciting attitudes of clinicians to the diagnosis of a variety of conditions. It provides a measure of the concern the physician has over misdiagnosing a particular condition and relates, of course, to the nature of the condition and the available treatments.

To conclude, the difficulties of diagnosis in psychiatry have been considered, along with the relevance of diagnosis to management. Other factors, such as the psychiatrist's "set" have been reviewed. The complexities of the decision making process have been touched upon and examples of using an algorithm, Bayes' theorem, as a device to help understand clinical decision making, have been discussed. In the light of this re-evaluation of decision making, diagnosis and treatment, the next chapter will re-evaluate the literature on the development of the DST as a specific test for melancholia.

CHAPTER TWO:

THE DEVELOPMENT OF THE USE OF THE DST IN PSYCHIATRY:

1. Cortisol Levels in Psychiatric Disorders.

> "An important research area in psychosomatic medicine concerns the relationship of various emotional states to adrenal cortical activation".

Thus began Rubin and Mandell's[1] review of psychoneuroendocrinology in 1966. By the mid-'60s the success of physical treatment such as electroconvulsive therapy, neuroleptics and tricyclic antidepressants in treating psychoses, had given a firmer basis to the contention, held since Hippocrates formulated melancholia in terms of an imbalance of "humours", that some psychiatric disorders had a physical or organic basis.

In 1965 Schildkraut[2] had formulated the "biogenic amine hypothesis" of affective disorders. The hypothesis states that:

> "Some, if not all, depressions are associated with an absolute or relative deficiency of catecholamines, particularly norepinephrine, at functionally important synapses in the brain. Conversely, elation may be associated with an excess of such amines".

This "biogenic amine hypothesis" is based, in part, on observations that drugs such as mono-amine oxidase inhibitors and tricyclic antidepressants, which potentiate brain amines, cause activation and have an antidepressant effect. Conversely, drugs such as reserpine, which deplete brain amines, have a sedative or depressant effect.

THE DEVELOPMENT OF THE USE OF THE DST IN PSYCHIATRY

In their review, Rubin and Mandell described the work of Nauta[3], who had characterised the lateral hypothalamus as the nodal point in both the ascending and descending paths of the "limbic system mid-brain circuit", and the cells of the medial hypothalamus as a final common pathway for the influence of subcortical neuron nets on the endocrine system. The role of limbic system structures in the modulation of emotional behaviour had been known since the work of Papez[4]. Rubin and Mandell claimed that "the possibility of using endocrine-dependent variables as reflections of limbic system function in man may be an important new neurophysiological approach".

By 1966 adrenal cortical activity in several psychiatric disorders had been studied. The difficulty with much of this work was in deciding whether it was the "stress" of the psychiatric disorder or the psychiatric disorder itself which brought about the observed changes in adrenal activity.

Persky et al.[5] in a series of studies found that, in general, plasma and urinary levels of 17 hydroxycorticoids were greater in anxious, hospitalised psychiatric patients than in normal controls. Sachar et al.[6] studied four young males with schizophrenia with respect to urinary excretion of 17 hydroxycorticoids. They found that periods of heightened corticoid excretion were characterised by a breakdown of "psychological defenses". They

hypothesised that corticoid excretion was influenced not by the type of defense, viz., neurotic or psychotic, but rather by its effectiveness against anxiety.

With respect to affective disorders, several studies of adrenal function in depression and mania had been made by the mid-'60s. They had generally revealed increased production of corticoids during depression. Some studies, such as that of Gibbons[7], had shown a return to normal levels after treatment with ECT or antidepressants. Bunney et al.[8] studied a 43-year-old woman with a rapid cycling bipolar affective disorder. Consistent decreases in 24 hour urinary 17 hydroxycorticoids on this patient's manic days and consistent increases on the depressed days were reported. Absolute levels of 24 hour excretion on all days were always within limits of normal variation, but the day to day fluctuations were consistent and there were statistically significant differences between manic and depressed days. Like Sachar et al., Bunney et al. viewed the increased steroid excretion on the depressed days as a concomitant of decreased psychological defense strength against anxiety, while the decreased steroid excretion on manic days reflected an absence of anxiety and a lack of "awareness of illness".

This notion of the "stress" of the psychiatric disorder and not the disorder itself, leading to alterations in cortico-adrenal activity, was to hold sway in the literature for some years, although, as will be

discussed later, Rubin and Mandell did offer alternative hypotheses. Bunney and Faucett[9] had demonstrated high mean levels of 17 hydroxycorticosteroid levels in three patients who committed suicide, but had showed relatively low clinical ratings of suicidal behaviour, an observation which tended not to fit the above hypothesis. Rubin and Mandell suggested that perhaps the variations in corticosteroid levels seen in some psychiatric disorders might be affecting, if not causing, the emotional state itself. They went on to discuss the psychological changes reported in patients with Cushing's disease, and to describe the depression, apathy and suicidal ideation seen in many patients. They commented: "Depression may be a central nervous system response to high circulating gluco-corticoids". They then commented on a further possibility, that "functional depressive states are concomitants of a supra-hypophyseal brain dysfunction which is also responsible for hyperstimulation of the anterior pituitary". In other words, they were suggesting that hypercortisolism might be a specific symptom of certain depressive illnesses.

2. The DST and Affective Disorders.

Dexamethasone suppression tests (DST) were used widely by the mid-'60s to help establish a diagnosis of Cushing's syndrome. Liddle[10] had reported in 1960 that low doses of dexamethasone, which would lead to suppression of

cortisol in normal subjects, did not suppress cortisol in patients with Cushing's syndrome, thus indicating a disturbance in the feedback control of corticotrophin release.

In 1968 Butler and Besser[11] reported the results of dexamethasone suppression tests before and after treatment in three patients with severe "primary affective disorder" who were otherwise physically healthy. Butler found in his three depressed patients a resistance to dexamethasone suppression similar to that seen in Cushing's syndrome; however, after treatment with a combination of ECT and antidepressants, this abnormality was not present. Butler commented that "since severe depression may be a presenting feature of Cushing's syndrome, diagnostic confusion could arise in patients with primary affective disorder".

In the same year Carroll et al.[12] reported the results of dexamethasone suppression tests (DST) in a series of 27 patients with severe depressive illnesses, before and after recovery, and in a control group of 22 patients with other psychiatric disorders. In this study blood samples for estimation of 11 hydroxycorticosteroid (11-OHCS) were taken at 8.30 a.m. and 4.30 p.m. Dexamethasone phosphate 2 mg was given orally at midnight and a further plasma sample taken at 8.30 a.m. the next day. The mean 11-OHCS levels at 8.30 a.m. after dexamethasone were 13.1 (ug/100 ml) (SD 7.0) in the

depressed patients, 5.3 (ug/100 ml) (SD 5.1) in the recovered depressed patients and 4.8 (ug/100 ml) (SD 3.7) in the non-depressed patients. The difference between the depressed and non-depressed patients was significant at the 0.001 level. The levels of 11-OHCS in each group of patients at 8.30 a.m., prior to dexamethasone, were not significantly different. Carroll et al. commented that the results showed that the dexamethasone suppression test (DST) discriminated between two groups of patients (depressed and non-depressed) who have identical basal morning plasma 11-OHCS levels. They highlighted the inadequacy of single estimation of plasma levels of 11-OHCS as an index of pituitary-adrenal function.

In 1971, in a study of 24 patients with various psychiatric disorders, Shopsin and Gershon[13] were unable to replicate Carroll's findings. They also found higher morning cortisol levels in schizophrenic patients compared with depressed patients. They were unable to explain the disparity between their findings and Carroll's. They underlined the critical need for:

> "considering an individual's perception of, and adjustment to, stress when evaluating the significance of steroid activity as related to psychiatric diagnostic entities".

They supported the notion that the non-specific "stress" of the psychiatric disorder produced any observed changes in corticosteroid levels.

THE DEVELOPMENT OF THE USE OF THE DST IN PSYCHIATRY

Sachar et al.[14], who favoured the explanation that increased adrenocortical secretion was not a characteristic of depressive illness per se, but rather was associated with "affective arousal" and "psychotic decompensation" which may be associated with depressive illness, produced evidence to support this view in 1970. They studied cortisol production in 16 depressed patients before and after recovery by infusing intravenously C14 tagged cortisol and measuring urinary metabolites. They also rated each patient with a Depressive Symptom Rating Form, a schedule which rated "depressive symptoms" and "affective arousal" and "psychotic disorganisation". They found that changes in cortisol production following recovery from depressive illness correlated well with changes in scores for "affective arousal" and "acute psychotic decompensation" but correlated poorly with changes in "depressive symptomatology". Sachar et al. felt that previous reports of high levels of corticosteroids in depressed patients normalising on recovery were attributable to a confusion in psychiatric nosology; i.e., a confusion in deciding what were depressive symptoms and what was affective arousal.

In 1973 Sachar et al.[15] went on to investigate the complex nature of cortisol secretion in normals, using a technique of sampling blood through a venous cannula every 20 minutes over a 24-hour period. These studies revealed that in normals cortisol is secreted in about eight major

episodes each day, with sharp rises and falls in plasma cortisol concentration. They then studied patterns of cortisol secretion using this technique in depressed patients. Their findings led them to revise the formulation that cortisol hypersecretion in certain depressive illnesses was simply a stress response. They found that depressed patients, while ill, secrete more cortisol, had more secretory episodes and more minutes of active secretion. Cortisol was actively secreted during late evening and early morning when normally secretion is minimal. After treatment, the depressed patients' secretory patterns normalised. Sachar et al. commented that animal studies had shown that episodic secretion of cortisol closely parallels episodic secretion of adrenocorticotropic hormone (ACTH), and as the half life of cortisol in his depressed patients was normal, then the disturbance in the 24-hour secretory pattern was almost certainly due to a change in the central nervous system programme regulating ACTH secretion. Thus Sachar et al. now saw the hypersecretion of cortisol in certain depressive illnesses not simply as a stress response, but rather as reflection of apparent limbic system dysfunction, along with other disturbances of mood, appetite, sleep and autonomic nervous system activity.

In 1976 Carroll[16] published a study which gave further support to the hypothesis that changes in corticosteroid secretion seen in some depressive illnesses were not due

to the non-specific stress of "psychological ego defense breakdown". He studied a group of patients with primary depression and a group with schizophrenia, comparing cortisol levels and response to dexamethasone in each group. Both groups showed a high level of "ego defense breakdown" as measured by Sachar's criteria. The depressed patients had elevated free cortisol excretion, high cortisol CSF levels and did not show normal suppression in response to dexamethasone. Despite the presence of severe ego defense breakdown and some secondary depressive symptomatology, the schizophrenic patients had normal hypothalamic-pituitary-adrenal function. Carroll concluded from this study that there was a hypothalamic limbic system dysfunction occurring in some depressed patients with primary depressive illness, and that this dysfunction was similar, but less severe, than that occurring in Cushing's disease. The results lent support to the early hypothesis of Rubin and Mandell.

Also in 1976, Carroll et al.[17] reported the findings of a study where the effect of dexamethasone in patients with primary depression was monitored using venous cannula techniques. Blood samples were taken every 30 minutes for 24 hours before and after dexamethasone 2 mg was given. Carroll et al. were investigating the importance of the time course of the suppression response in detecting what they assumed to be a subtle abnormality of hypothalamic pituitary adrenal function occurring in depression. In

other words, if more frequent blood samples were taken on the day after dexamethasone, then possibly these abnormalities might be detected. In fact, the catheter studies revealed an "early escape" from suppression, rather than an absolute resistance to suppression by dexamethasone in depressed patients. Often a pattern of "initial suppression" was followed by this "early escape" from dexamethasone suppression. Carroll et al. felt that this finding was able to explain the negative findings of Shopsin and Gershon's study, where a single morning blood sample was the sole index of suppression.

Carroll et al.[18] also reported on the results of dexamethasone suppression tests in a series of 42 patients with "endogenomorphic depression" and 42 patients with other psychiatric disorders. The DST procedure in this series included a 2 mg dose of dexamethasone given at 11.30 p.m. and plasma samples taken at 8 a.m., 4 p.m. and 11.30 p.m. the following day. Urine samples were also taken. Cortisol was measured using a competitive protein binding method. The endocrine literature was reviewed to obtain criteria for judging whether measured cortisol values were abnormal. Patients taking phenytoin or phenobarbital were excluded because of these drugs' effects on dexamethasone metabolism. They found the plasma and urinary cortisol results before dexamethasone administration did not distinguish the endogenous depressive group very effectively. The cortisol values after dexamethasone were

considerably more powerful as discriminators between the endogenous and the "other" group. About half the endogenous group had abnormal suppression and at least one post-dexamethasone sample, and no patient with a depressive neurosis had an abnormal result. On the basis of these results Carroll et al. claimed "We wish to call attention to this test as a promising laboratory aid in the diagnosis of 'endogenous' depressive states".

In 1979 Brown et al.[19] were able to replicate Carroll's findings. In a series of 54 patients given the DST, they found that 40% of those with a diagnosis of major depression were non-suppressors after dexamethasone. They used a similar protocol for the DST as in Carroll's 1976 study. None of the patients with other psychiatric diagnoses had abnormal suppression. Similarly, Brown et al. found that the 11.30 p.m. blood sample identified the highest proportion of patients with endogenous depression. Brown et al. were not able to identify any differences in symptom patterns between those patients with major depression who did suppress after dexamethasone and those who did not. They found a higher proportion of those who did not suppress (57%) responded well to treatment than in those who did suppress (20%).

Nuller and Ostroumova[20] in 1980 published a report on dexamethasone suppression in 52 patients with endogenous depression and a control group. They attempted to increase the sensitivity of the test for depression by reducing the

dose of dexamethasone to 0.5 mg. Using this technique they found 69% of the group with endogenous depression were resistant to dexamethasone suppression, while 9% of the control group showed resistance to suppression. They reported the normalisation of dexamethasone suppression when their depressed patients were in remission.

3. A Standardised Form of the DST.

In 1981 Carroll et al.[21] published an article entitled "A Specific Laboratory Test for the Diagnosis of Melancholia, Standardisation Validation and Clinical Utility". They began by stating that "An objective laboratory procedure to assist in making the diagnosis of melancholia would be useful" considering the longstanding difficulty in differential diagnosis between melancholia and non-endogenous depression.

The paper reported the results of the DST in 438 subjects, 215 of whom had a diagnosis of melancholia. Diagnoses were made by consensus by an interviewer, who had administered the Schedule for Affective Disorders, and a psychiatrist. These clinical diagnoses were supported by RDC diagnoses in 95% of cases. The prevalence of melancholia in the group was 58%. Severity of depressive symptoms was also assessed. Exclusion criteria included patients who were undiagnosed (2%), who had schizo-affective disorder and those with borderline personality disorder. Medical exclusion criteria included concurrent administration of

drugs known to affect dexamethasone metabolism, pregnancy, severe weight loss, uncontrolled diabetes mellitus, major physical illness, temporal lobe epilepsy, acute alcohol withdrawal, high dose barbiturates and endocrine disease. Both inpatients and outpatients were included. The dose of dexamethasone administered was either 1 mg or 2 mg. Blood was obtained at 11.30 p.m. prior to dexamethasone and at 8 a.m., 4 p.m. and 11.30 p.m. the following day. In the outpatient sample only the 4 p.m. post-dexamethasone sample was obtained. Plasma cortisol was assayed using competitive protein binding techniques.

A bimodal pattern of 4 p.m. cortisol values was found with non-melancholic patients having plasma cortisols below 5 u gm/ d L. Almost all patients with values above 5 u gm/ d L at 4 p.m. were diagnosed as melancholic. Carroll et al. suggested 5 u gm/ d L as a criterion value for the diagnosis of melancholia. They found amongst a sample of 70 normal subjects about 4% had non-suppressing results; this rate was similar to that in patients who did not have melancholia. They found that lowering the dose of dexamethasone from 2 mg to 1 mg increased the sensitivity of the test from 39% to 67% without affecting the specificity. They found that the 11.30 p.m. pre-dexamethasone cortisol level was not highly specific for melancholia. There was no difference in the proportion of males or females with melancholia who were detected by the test.

THE DEVELOPMENT OF THE USE OF THE DST IN PSYCHIATRY

Carroll et al. saw as evidence for the face validity of the DST its high specificity and predictive value. Further evidence for face validity came from the increasing number of non-suppressing results, with increasing "certainty of diagnosis" of melancholia. Predictive validity was reflected in the failure of conversion to normal of the DST being associated with early relapse. Construct validity was demonstrated by the reversion to normal of the test with treatment. Carroll et al. stated that construct validity also came from the fact that the neuro-endocrine abnormality revealed by the DST indicates dysfunction in the hypothalamus and the limbic system, the proposed site of dysfunction in the affective disorders. Thus 16 years after Rubin and Mandell's comments about the nature of cortisol hypersecretion in some depressive illnesses, the DST was reported as a simple laboratory test for endogenous depression with considerable utility and validity.

4. Use of the DST in Psychiatry in Recent Times.

In the last three years a large number of publications has appeared examining the DST and its application to clinical psychiatry. A non-exhaustive medline search of the literature on the DST and its application to psychiatry revealed a dramatic increase in the number of publications in the period 1979-83, in comparison to the previous decade. The following section will review some of these publications.

THE DEVELOPMENT OF THE USE OF THE DST IN PSYCHIATRY

In 1981 Asnis and Sacher et al.[22], whose previous work had shed much light onto the complexities of cortisol hypersecretion in depression, reported on the ability of the DST to uncover cortisol hypersecretion in depressed patients. The assumption tested was that resistance to dexamethasone suppression was a reflection of increased hypothalamic-pituitary-adrenal activity. Asnis and Sacher found that the DST was a highly specific test for cortisol hypersecretion, but that it was not very sensitive in that only 50% of cortisol hypersecreters (confirmed by cannula studies) showed resistance to dexamethasone. They used 2 mg of dexamethasone in their DST and they suggested that a lower dose may have increased the sensitivity of the test for cortisol hypersecretion, the presumed "parent abnormality" in depression. Asnis and Sachar[23] have more recently produced evidence showing that amongst endogenously depressed patients cortisol hypersecretion was highly correlated with shortened REM latency, another presumed marker of biological depression. They hypothesise that a noradrenergic deficit or a cholinergic excess may be responsible for the association of cortisol hypersecretion and shortened REM latency in biological depression.

Concurrent with the development of the DST, other neuro-endocrine disturbances occurring during depression have been investigated by Prange and Loosen[24] and others. In particular, it has been noted that 25-35% of endogenously depressed patients have a blunted thyrotropin (TSH)

response to intravenous administration of thyrotropin-releasing hormone (TRH). Targum et al.[25] reported in 1982 that by performing the TRH test and the DST, the combined sensitivity of both tests in identifying major depressive disorder was 67% with 92% specificity. They found that only 11% of their sample of 54 depressed patients had both abnormal DST and TRH responses, suggesting that the hypothalamic-pituitary-adrenal dysfunction and the hypothalamic-pituitary-thyroid dysfunction, which occur in depression, were independent phenomena.

Initial reports of the use of the DST were based on inpatient populations. Several studies have reported on the use of the DST in outpatients. Jaffe et al.[26] reported the DST to be positive in three out of seven outpatients diagnosed as having major depression with melancholia. None of 15 patients with major depression without melancholia had a positive DST. Other authors, Peselow et al.[27] and Rabkin et al.[28] have not found the DST to be a sensitive diagnostic indicator for endogenous depression in larger outpatient populations. Peselow et al. in 1983 did report a statistically greater frequency of abnormal DSTs in depressed outpatients than in normal controls.

Over the last three years a number of reports have appeared where the DST has been used to give "objective support" to classification systems of depressive illness. Carroll had always stressed the specificity of the DST for the endogenous sub-group of depressive disorders. In a

replication study of Carroll's 1976 findings, Schlesser et al.[29] found resistance to dexamethasone in 43% of their 86 depressed patients and in none of their 80 controls who had other psychiatric disorders. They classified the depressed patients into those with either "familial pure depressive disease (FPDD)" or "sporadic depressive disease (SDD)" or "depressive spectrum disease (DSD)" following the classification system of Winokur for primary unipolar depression. This schema has been supported by clinical and genetic evidence. Schlesser et al. found the greatest percentage of non-suppressors in the FPDD group (82%), and the SDD group had 37% non-suppression and only 4% of the DSD group had non-suppression. Schlesser's findings of a greater proportion of non-suppressors in FPDD than in DSD were supported by a series reported by Targum et al.[30] in 1982 and by Coryell et al.[31] in 1982. However, Rudorfer et al.[32] reported they had been unable to replicate the findings of Schlesser et al. that there was a higher rate of DST non-suppression amongst patients with family pure depressive disorder, FPDD, than in depression spectrum disease, DSD, or in sporadic depressive disorder, SDD. Rudorfer et al. found the highest rate of non-suppression in the SDD group. Kasper and Beckman[33] similarly found that DST non-suppression was not more prevalent in FPDD patients.

Schatzberg et al.[34] reported significantly higher rates of non-suppression in unipolar as opposed to bipolar depression. They also found significantly higher levels

of post-dexamethasone in patients with depression and psychosis compared with those depressed patients without psychosis. Evans et al.[35] similarly found significantly higher post-dexamethasone cortisol levels in patients with major depression with psychosis.

Coryell and Schlesser[36] examined any relationship between suicide and DST non-suppression. Earlier Bunney and Fawcett (see p.30) had reported an association between suicidal behaviour and high levels of urinary 17 OHCS. They reviewed 243 patients with unipolar depression who had been given DSTs. Over a period of three years, five of these patients committed suicide. Of these five, four had been diagnosed as having primary depression and each had had abnormal DST responses. None of the remaining 109 patients with primary depression committed suicide. The fifth patient who committed suicide had been diagnosed as having a secondary depression; her DST response was normal. In 1983 Targum et al.[37] reported a significant association between attempted suicide and abnormal DST in a group of 49 inpatients with Research Diagnostic Criteria (RDC) diagnoses of primary unipolar depression.

That endogenous depression may be difficult to diagnose on phenomenological grounds alone is well-known, and the development of concepts such as "masked depression" reflects this difficulty. Several reports have addressed the issue as to whether the DST could act as "symptom independent" objective marker of depression where the symptom pattern was confusing or atypical.

THE DEVELOPMENT OF THE USE OF THE DST IN PSYCHIATRY

Greden and Carroll[38] reported on the efficacy of the DST in identifying an underlying affective disorder in patients with catatonia. They reported a single case where a woman with features of catatonia had abnormal dexamethasone suppression. She was successfully treated with ECT and lithium carbonate. The use of ECT, a treatment generally found most effective in endogenous depression, in successfully treating catatonia, is well established. The presence of similar and identifiable neuro-endocrine dysfunctions in both catatonia and depression appeared to give a rationale to the effectiveness of ECT in catatonia.

Evans and Nemenoff[39] and Krishnan et al.[40] have reported rates of abnormal dexamethasone suppression in mixed bipolar disorder similar to those occurring in endogenous depression. Targum[41] reported higher rates of neuro-endocrine dysfunction (abnormal DST or abnormal TRH response) in patients who went on to have complete recovery from an acute schizophreniform disorder. Gwirtsman et al.[42] have reported a 67% rate of DST non-suppression in a group of patients with bulimia, none of whom was markedly underweight. In 1982 Blumer et al.[43] used a 50% non-suppression rate in a series of patients with chronic pain to support their contention that some forms of chronic pain are a variant of depressive disorders.

There are, of course, two lines of argument with respect to these findings. Firstly, it could be argued

that some forms of mixed bipolar disorder, bulimia, schizophreniform disorder and chronic pain disorder are symptomatic manifestations of an "underlying" disorder. The alternative explanation is that the DST is simply not highly specific for depression.

Reus[44] has reported on the use of the DST as the independent variable in a group of 118 psychiatric inpatients. Reus states, in a manner reminiscent of Claude Bernard (see p.15):

> "This approach derives from the belief that the biological variable under examination may possess more clinical relevance than that provided by the global diagnostic label, much in the same way as a sputum culture provides more information about cause, course, and appropriate treatment of pneumonia than that afforded by the clinical diagnosis, with its attendant signs and symptoms".

Reus found that, regardless of diagnosis, failure to suppress cortisol following the DST identified patients with an increased incidence of sleep disorder, feelings of anxiety and thoughts of suicide.

Ward et al.[45] reported in 1982 a single case study where the results of the DST were useful in the treatment of a 64-year-old woman with a history of an affective disorder who presented with symptoms suggestive of paraphrenia. They reported "uncertainty about her diagnosis led to uncertainty about which treatment to pursue". She made little response to three ECT treatments; at this stage a DST non-suppressing result was obtained:

"The DST provided a greater degree of diagnostic certainty" that ECT should continue. The patient made a good response with seven ECTs. The authors commented: "If a patient with paranoia and a history of depression demonstrates non-suppression on the DST, the clinician might reasonably treat the patient with antidepressants or ECT and feel confident this course of action should be aggressively pursued".

Several psychiatric conditions appear to respond to treatments generally considered specific for other psychiatric conditions. For example, patients with panic attacks and agoraphobia have been reported to respond to antidepressants such as imipramine and phenelzine. In 1982 Curtis et al.[46] reported a series of 20 patients with agoraphobia and panic attacks who had received DSTs. They found three patients with abnormal DST results and they attributed these results to alcohol withdrawal (two patients) and concurrent depression (one patient). Thus they concluded that, while patients with panic attacks and agoraphobia may respond to imipramine or phenelzine, "antidepressant" medication, there was no neuro-endocrine dysfunction suggestive of an "underlying depression" in these patients. In 1983 Sheehan et al.[47] and Lieberman et al.[48] confirmed these findings.

Papers began to appear about this time reporting on the use of the DST as an index of recovery from depressive illness. Albala et al.[49] reported on changes in DST

response occurring during a course of ECT in patients who were depressed and were initially resistant to suppression. Six patients were studied; in five the DST response had normalised after 4-5 ECTs. The normalisation of the DST often occurred before significant clinical improvement was evident. The DST remained abnormal in the one patient who did not respond to the ECT. Albala et al. concluded that the DST was a "successful biological monitor of clinical response". However, these results were not confirmed in a preliminary report by Decina et al.[50] in 1983. In a further report, Greden et al.[51] examined outcome in patients who, while they had shown clinical improvement after treatment, remained DST resistant in comparison with patients who showed both clinical improvement or reversion to DST suppression after treatment. The "non-normalisers" had a significantly poorer outcome, with more relapses and rehospitalisations. The authors suggested that a DST performed prior to discharge may enable the clinician to decide on the most appropriate course of management: "If the repeat DST is abnormal, clinicians should be skeptical recovery has occurred". Goldberg[52] reported similar findings and stated: "I strongly urge physicians to have both clinical and neuro-endocrine evidence of remission before discontinuing antidepressant therapy". Greden et al.[53] reported in 1983 on the use of serial DSTs to monitor improvement in a group of 31 depressed patients treated pharmacologically. They found that most

non-suppressors became suppressors in conjunction with clinical improvement, that DST normalisation often preceded clinical improvement and that failure to normalise was often associated with poor clinical outcome.

The effects of various antidepressants on the DST have also been investigated. Amsterdam et al.[54] investigated any confounding effects tricyclics may have on the DST. A group of 12 patients with primary affective disorders, who were initially suppressors prior to tricyclic antidepressant treatment, remained suppressors three weeks after treatment with the drug. It was thus concluded that tricyclics induced no false positive DST results.

In a preliminary report, Brown et al.[55] found that non-suppressing patients with depression responded significantly better to imipramine and desipramine than to amitriptyline or clomipramine. The reverse was true for the group of depressed patients who were suppressors. Brown et al. hypothesised that DST non-suppressors have a noradrenergic deficiency and thus respond preferentially to imipramine and desipramine, drugs which are said to have a predominant effect on noradrenergic systems. DST suppressors, meanwhile, have a serotonergic deficiency and respond better to amitriptyline or clomipramine, drugs with predominantly serotonergic effects. Fraser[56] reported similar findings in 1983 in a retrospective study where non-suppression on the DST predicted good response to noradrenergic antidepressants. Greden et al.[57] were

unable to replicate these findings. In a study of 26 non-suppressing depressed patients treated either with imipramine or amitriptyline, they found no significant differences in outcome. They concluded that the DST was not able to assist in the choice of a particular tricyclic antidepressant in the treatment of depression.

In a group of 34 patients with primary major depression (RDC) Brown and Brawley[58] administered the DST and a methylphenidate challenge. They found the two tests divided patients into two groups: one group failed to suppress cortisol and failed to respond to methylphenidate with a transient mood elevation; the other group suppressed cortisol and did respond to methylphenidate transiently. In an open trial the former group responded to amitriptyline and the latter group to imipramine. Brown and Brawley commented that the association between methylphenidate non-response and cortisol non-suppression is surprising if methylphenidate non-response is taken to indicate noradrenaline "dysfunction". They added that explanations of complex regulatory functions like CRF secretion in terms of a single neurotransmitter abnormality are likely to be misleading. In 1983 Jimerson et al.[59] reported a robust correlation between post-dexamethasone levels of cortisol and plasma MHPG after dexamethasone, a result not supporting the hypothesis that "noradrenergic" antidepressants should be more effective in dexamethasone non-suppressors.

5. Problems with the Use of the DST in Psychiatry.

Along with the increasing number of publications indicating the utility of the DST as a laboratory test in depression, there has also been a growing number of reports, particularly within the last year, which call for caution in the interpretation of results of the DST in clinical psychiatry.

In a study of the DST in 53 healthy volunteers, Amsterdam et al.[60] reported 15.1% showed non-suppression. They commented on the fact that the incidence of early escape from suppression after dexamethasone has not been extensively investigated and he added that "for data obtained from the DST to have validity and interpretability, appropriate internal controls must be employed". Hallstrom et al.[61] reported 19% of women given the DST in a population study had non-suppressing results. There were no differences between suppressors and non-suppressors with regard to depressive symptoms.

The high specificity for melancholia or endogenous depression was a factor in making the DST an attractive laboratory diagnostic aid. In 1982 Spar and Gerner[62] called this high specificity into question in a report where they performed the DST on 17 patients with a DSM III diagnosis of dementia. None of the patients met DSM III criteria for major depressive illness. Nine of the 17 had abnormal DST results and thus Spar and Gerner suggested the DST be used with caution in distinguishing dementia from depression in the elderly. Balldin et al.[63]

similarly found abnormal DST results to be related to dementia and not to age or depression in a study of patients with Alzheimer's disease, multi-infarct dementia and healthy controls.

Targum and Capodanno[64] in 1983 reported the predictive value of the DST for major depressive disorder in adolescents to be only 28%. Geller et al.[65] reported that only two of 14 children aged 5-12 years with DSM III major depression were non-suppressors. These studies indicate that the usefulness of the DST as a diagnostic aid in patients where diagnosis is difficult, viz. children, adolescents and the elderly, may be limited.

Coppen et al.[66] reported on the prevalence of abnormal response to dexamethasone in a group of psychiatric inpatients and normal controls. Eleven per cent of controls had abnormal responses. Abnormal responses were found in 70% of depressed patients, 20% of schizophrenic patients, 25% of abstinent alcoholics, 40% of patients with neurotic disorders and 50% of patients with dementia. Diagnoses were made using the ICD-9 system. Holsboer et al.[67] reported a sensitivity of 23.7% and specificity of 86% for abnormal DST results for endogenous depression (ICD-9). They found 14.7% of patients diagnosed as reactive or neurotic depression showed non-suppression. The DST in this series consisted of 2 mg dexamethasone with a blood sample for cortisol taken at 4 p.m. They found that the severity of the depression correlated well

with non-suppression, regardless of the diagnostic classification, either endogenous or reactive. They thus concluded abnormal DST status appeared of "limited predictive value for correct diagnosis".

Meltzer et al.[68] in 1982 similarly reported a specificity of only 76.9% for primary depression, a figure below that previously reported.

Winokur et al.[69] examined the response of a group of 12 patients with primary depressive disorder and a control group to a series of four neuro-endocrine challenges - thyrotropin-releasing hormone (TRH), gonadotrophin-releasing hormone stimulation, insulin tolerance test (ITT) and overnight dexamethasone suppression test (DST). They found that 96% of the depressed patients had at least one abnormal response, while 29.2% of the control group had at least one abnormal response. They found that non-suppression after dexamethasone occurred as frequently in the control group (8.3%) as in the depressed group (7.7%). There were no consistent patterns of abnormalities. The authors suggested that the hormonal responses in depressed patients "are most accurately defined in terms of their variability with respect to responses seen in healthy subjects".

In 1983 Edelstein et al.[70] reported on post-dexamethasone cortisol secretion in obese, depression-free patients before and after weight loss. All suppressed before

weight loss; however, 27% failed to suppress after an average loss of 13.5 kg. Failure to suppress was not associated with changes in depression ratings. They commented that in depressed patients with weight loss of nine or more kilograms, DST confirmation of diagnosis should not be relied on.

Newsom and Murray[71] reported on the DST in detoxified alcohol abusing inpatients. Thirteen of 75 patients were non-suppressors after intoxication; all had reverted to normal suppression after four more weeks of abstinence. No patients met DSM III criteria for major depression, although all had initial subjective complaints of depression.

Other reports have questioned the methods of performing the DST. Meltzer and Fang[72] reviewed various methods of cortisol determination in current use and found significant discrepancies. The most widely used method,the radio-immuno assay method, may not produce levels comparable to those produced by the competitive protein binding method. Meltzer and Fang comment: "The use of the DST by physicians should be preceded by an assessment of the validity of the cortisol level determinations in the critical range for the DST by the laboratory they use". Brown et al.[73] reported on variations in results produced by using either 1 mg or 2 mg of dexamethasone. Goggans et al.[74] reported on increasing the sensitivity of the DST by increasing the number of cortisol sampling time points.

THE DEVELOPMENT OF THE USE OF THE DST IN PSYCHIATRY

A case report of Amsterdam et al.[75] in 1982 questioned the use of the DST as a prognostic tool to predict future depressive episodes. In the case reported a patient, a non-suppressor, reverted to a suppressor after treatment with antidepressants. Ten months after treatment she relapsed; a DST performed at this stage showed her to be a suppressor. The case raised the question as to whether DST non-suppression occurs with each relapse for a particular patient. If a non-suppressor during one episode of depression could be a suppressor during the next episode, then the prognostic value of the reversion of the DST would be limited. Coryell and Schlesser[76] reported in 1983 on DST results in patients during several different hospitalisations for depression. They found 40.9% of patients who were DST non-suppressors on one admission were suppressors on the other admission. They commented that abnormal escape from dexamethasone may only partially overlap the depressive syndrome in time.

Carroll[77] discussed the interpretation of DST results in a review article in 1982. In particular, he drew attention to the fact that the "diagnostic confidence" of an abnormal test result was 94% in a population where the prevalence of endogenous depression was 50%. With a lower prevalence, the diagnostic confidence or predictive value of the test is decreased. He therefore suggested that the test not be recommended as a screening procedure for all psychiatric patients and urged that clinicians

avoid over-interpreting the test results. Baldessarini et al.[78] in 1983 discussed the predictive power of diagnostic tests in psychiatry and the effect of prevalence of illness. They commented that "basic statistical principles required for critical evaluation of their value remain poorly integrated into clinical thinking".

To conclude, evidence for the hypothesis that a sub-group of depressed patients has a specific neuro-endocrine abnormality, has been reviewed. The use and popularity of the DST to measure this abnormality has been described. The increasingly large literature on the use of the DST as a diagnostic tool, an index of recovery and a prognostic tool in the management of depression, has been reviewed. Finally, the recent cautionary literature commenting on the need for care in interpreting DST results has been discussed.

CHAPTER THREE:

A RETROSPECTIVE STUDY OF THE IMPACT OF THE INTRODUCTION OF THE DST ON THE DIAGNOSIS AND MANAGEMENT OF PSYCHIATRIC INPATIENTS:

1. Introduction.

The following study is not concerned with the diagnostic accuracy of the DST for melancholia, nor is it concerned with the nature of possible limbic system abnormalities which might be reflected by abnormal cortisol production in depression. It is rather concerned with the effects of the introduction of this laboratory procedure into clinical psychiatry. More specifically, was the introduction of the DST associated with any changes in diagnostic practice or treatment?

The DST was introducted to the Psychiatric Unit of the Royal Adelaide Hospital in March 1981, a few months after Carroll et al.[1] had reported on the utility of a standardised form of the DST. Within the Psychiatric Unit of the Royal Adelaide Hospital use of the DST was generally encouraged, particularly in cases where biological depression was suspected but difficult to diagnose on purely phenomenological grounds. There was no expectation that significant changes in diagnosis or treatment would have occurred with the introduction of the DST. To test this hypothesis a review of inpatient notes was performed. This review permitted comparisons of clinicians' behaviour with respect to diagnosis and treatment before and after March 1981.

A RETROSPECTIVE STUDY OF THE IMPACT OF THE INTRODUCTION OF THE DST ON THE DIAGNOSIS AND MANAGEMENT OF PSYCHIATRIC INPATIENTS:

2. Method.

Case-notes of patients at the psychiatric unit of the Royal Adelaide Hospital were reviewed.

The psychiatric unit at the Royal Adelaide Hospital (a 900-bed general hospital) consists of a 24-bed ward. Patients are referred from other wards in the hospital, the emergency service of the hospital or from psychiatric outpatients. A range of both somatic and psychosocial therapy is provided. The average length of stay[2] in the ward is 19 days.

The two periods of the study were from March to December 1980 prior to the introduction of the DST, and from March to December 1981. A list of all patients admitted during the periods was compiled from the ward bed-state register. Details on over 90% of these patients were retrievable from their case-notes. Information abstracted from the case-notes included: age, sex, previous psychiatric management, whether suicidal behaviour had occurred, a depression rating score, the Levine-Pilowsky Depression Score (LPD),[3] the DST result, treatment during admission and on discharge, and the final clinical diagnosis.

The Levine-Pilowsky Depression Questionnaire was routinely completed by patients on admission to the psychiatric unit at the Royal Adelaide Hospital. The questionnaire consists of 57 items requiring a yes or no

answer. It is self-administered. The questions relate both to psychological and physiological components of depression and are based on statements related to endogenous and neurotic depression in standard psychiatric tests. The questionnaire yields a measure of the severity of depression on a 20-point scale. It also allows for a classification of patients into three groups: non-endogenous depression, endogenous depression and no depressive syndrome present. The statistical method of numerical taxonomy is used to give the most parsimonious method of grouping patients on the basis of their responses to the questionnaire, thus forming the three LPD "classes".

The final clinical diagnosis was that made by the treating trainee psychiatrist when writing the discharge summary at the completion of treatment. These diagnoses were a combination of ICD-9 diagnoses, some DSM III diagnoses and some local variations of both systems. To overcome the problem of multiple diagnostic terms being used in the reviewed case-notes, the recorded diagnosis was allocated to one of four classes (Table 3.1). This allocation was made solely on the basis of the discharge diagnosis. In the results which follow the term "biological depression" was applied to classes a + b combined.

A RETROSPECTIVE STUDY OF THE IMPACT OF THE INTRODUCTION OF THE DST ON THE DIAGNOSIS AND MANAGEMENT OF PSYCHIATRIC INPATIENTS:

TABLE 3.1

Classification of final psychiatric diagnosis

Class	Diagnostic terms used at discharge
a	melancholia
	endogenous depression
	psychotic depression
	unipolar depressive illness
	depressed phase manic depressive illness
b	mixed depressive illness
c	neurotic depression
	reactive depression
	dysthymic disorder
	abnormal grief reaction
d	all other diagnostic terms.

From March 1981 a version of the DST protocol similar to that of Carroll was used at the Royal Adelaide Hospital: 1 mg dexamethasone phosphate was given orally at 11.00 p.m. on day 1. On day 2 blood was drawn for cortisol estimations at 8.00 a.m., 4.00 p.m. and 11.00 p.m. Cortisol levels were assayed using a radio-immuno assay technique (Amerlex, Amersham Kit). A plasma cortisol result greater than 160 nmol/l in any of the three samples was taken as a non-suppressing result; that is, a positive DST result.

This cut-off point differs from that suggested by Carroll who suggests 138 nmol/l (5 ug/dl). It is the cut-off point used at the Institute of Medical and Vetinary Science in Adelaide. It was deduced from probit analysis of local patient data and validated by data obtained locally from normals. All cortisol assays were performed at the Institute of Medical and Vetinary Science. Carroll's exclusion criteria for medical conditions and drug treatment, where the DST was likely to be misleading, were applied. The DST was usually performed within 2-3 days of admission.

3. Statistical Analysis.

For nominal data the chi square (X^2) test was used to determine whether a significant difference existed between the observed data in each category and that expected if there were no differences between groups.

Any differences in diagnosis or treatment between the two years might be accounted for by changes in the kinds of patients admitted. In particular, the effects of differences in age, sex, previous admission, suicidal behaviour and depression score were considered. In the chi-square values given for statistical tests of association, the Mantel-Haenszel[4] summary value is given where adjustment was required. Differences in LPD scores between years were analysed by T-test.

A RETROSPECTIVE STUDY OF THE IMPACT OF THE INTRODUCTION OF THE DST ON THE DIAGNOSIS AND MANAGEMENT OF PSYCHIATRIC INPATIENTS:

4. Results.

A total of 520 case-notes were reviewed, 258 in 1980 and 262 in 1981. In 1981, 162 patients were given the DST.

(a) Variations in case mix.

Historical comparisons are notoriously misleading. Possible differences in case mix over the two years which could account for the two periods studied were considered. In particular, the variables of age, sex, previous admission, suicidal act and depression score were considered. It would seem reasonable that variables such as previous admission, suicidal act and depression score could be associated with particular treatment and diagnosis; however, there was no major contribution of these factors to the variation in treatment and diagnosis over the period.

It did appear that age and sex variables were of importance, however. For example, when all patients from both periods under study were pooled, several factors with respect to the age of the patient and treatment and diagnosis became evident.

There was a significant association of antidepressant drug prescription with increasing age. For example, 17% of patients under 30 received antidepressants, while 63% of those over 50 received antidepressants. The number of

patients treated with antidepressants very closely approximates the number treated with a somatic antidepressant treatment, as most patients treated with ECT had a concurrent course of antidepressant medication.

TABLE 3.2

Variation of antidepressant treatment with age

Age (years)	Treatment		Total
	Given anti-depressants	Not given anti-depressants	
<30	27	134	161
30-50	71	106	177
>50	115	67	182
Total:	213	307	520

$X^2 = 76.19^*$ df = 2; p <.0001.

There was a significant association of diagnosis of biological depression with increasing age (Table 3.3). For example, 8% of patients under 30 received this diagnosis compared with 51% of patients over 50.

A RETROSPECTIVE STUDY OF THE IMPACT OF THE INTRODUCTION OF THE DST ON THE DIAGNOSIS AND MANAGEMENT OF PSYCHIATRIC INPATIENTS:

TABLE 3.3

Variation in diagnosis of biological depression with age

Age (years)	Diagnosis		Total
	biological depression (a + b)	all other diagnoses (c + d)	
<30	13	148	161
30-50	35	142	177
>50	93	89	182
Total:	141	379	520

$X^2 = 87.43^*$ df = 2; p <.0001.

There were significant differences in age distribution between the years (Table 3.4). For example, 29% of patients were aged between 30 and 50 in 1980, compared with 38% in the 1981 period.

A RETROSPECTIVE STUDY OF THE IMPACT OF THE INTRODUCTION OF THE DST ON THE DIAGNOSIS AND MANAGEMENT OF PSYCHIATRIC INPATIENTS:

TABLE 3.4

Variation in age distribution between consecutive years

Age (years)	Year		Total
	1980	1981	
<30	88	73	161
30-50	75	102	177
>50	95	87	182
Total:	258	262	520

$X^2 = 5.83^*$ df = 2; p <.05.

There was a trend towards more frequent diagnosis of biological depression in women than in men (Table 3.5). For example, 30% of women had this diagnosis compared with 22% of men.

A RETROSPECTIVE STUDY OF THE IMPACT OF THE INTRODUCTION OF THE DST ON THE DIAGNOSIS AND MANAGEMENT OF PSYCHIATRIC INPATIENTS:

TABLE 3.5

Variation in diagnosis by sex

Sex	Diagnosis		Total
	biological depression (a + b)	all other diagnoses (c + d)	
women	98	227	325
men	43	152	195
Total:	141	379	520

$X^2 = 3.65$ df = 1; $p > 0.05$.

There was a larger proportion of female admissions in 1980 compared with 1981. For example, 33% of the patient population was male in 1980, compared with 41% in 1981 (Table 3.6).

TABLE 3.6

Variation in sex distribution between years

Sex	Year		Total
	1980	1981	
Male	86	109	195
Female	172	153	325
Total:	258	262	520

$X^2 = 3.45$ df = 1; $p > 0.05$.

A RETROSPECTIVE STUDY OF THE IMPACT OF THE INTRODUCTION OF THE DST ON THE DIAGNOSIS AND MANAGEMENT OF PSYCHIATRIC INPATIENTS:

Previous admissions to a psychiatric unit did not significantly vary between the two periods of the study (Table 3.7).

TABLE 3.7

Variation in "previous admission" between 1980 and 1981

Previous Admission	Year		Total
	1980	1981	
No	192	189	381
Yes	66	73	139
Total:	258	262	520

$X^2 = 0.24$ df = 1; n.s.

Whether suicidal behaviour occurred did not significantly vary between the two periods of the study (Table 3.8).

TABLE 3.8

Variation in suicidal behaviour between 1980 and 1981

Suicidal behaviour	Year		Total
	1980	1981	
No	199	190	289
Yes	59	72	131
Total:	258	262	520

$X^2 = 1.2$ df = 1; n.s.

A RETROSPECTIVE STUDY OF THE IMPACT OF THE INTRODUCTION OF THE DST ON THE DIAGNOSIS AND MANAGEMENT OF PSYCHIATRIC INPATIENTS:

LPD scores were retrievable in only 60% of cases. The mean depression score which is an index of severity of depression was 10.7 in 1980 and 10.3 in 1981. There was no significant difference in LPD scores between 1980 and 1981 by T test.

There was no significant variation in the distribution of LPD classes between 1980 and 1981 (Table 3.9).

TABLE 3.9

Differences in LPD class between years

LPD class	Year		Total
	1980	1981	
1	23	41	64
2	53	66	119
3	49	85	134
Total:	125	192	317

$X^2 = 2.1$ df = 2; n.s.

Note: The LPD employs a decision rule to allocate patients to one of three classes; class 1 = non-endogenous depressive syndrome; class 2 = endogenous depressive syndrome; class 3 = non-depressive syndrome.

A RETROSPECTIVE STUDY OF THE IMPACT OF THE INTRODUCTION OF THE DST ON THE DIAGNOSIS AND MANAGEMENT OF PSYCHIATRIC INPATIENTS:

In summary, then, examination of "case mix" data from the two periods of the study revealed the following:

Five hundred and twenty case-notes were reviewed, 258 in 1980 and 262 in 1981. Age and sex were found to be confounding variables. There were significant differences in age distribution between the years. There was also a significant association of antidepressant drug prescription and diagnosis of biological depression with increasing age. There was a trend towards more frequent diagnosis of biological depression in female than in male patients, and there was a larger proportion of female admissions in 1980 than in 1981. Previous admission and suicidal behaviour did not vary significantly between years. There were no significant differences in LPD scores between years and no significant differences between LPD classes.

The variation in case-mix between the two years with respect to age and sex is corrected for in the following data using the Mantel-Haenszel test.[4] In the following data chi-square values are given, followed by a corrected chi-square value, corrected for age and sex. A value of chi-square of 3.84 indicates significance at the 5% level.

(b) Treatment and diagnostic practice.

The prescription of antidepressant drugs in the periods under question in 1980 and 1981 was examined.

A RETROSPECTIVE STUDY OF THE IMPACT OF THE INTRODUCTION OF THE DST ON THE DIAGNOSIS AND MANAGEMENT OF PSYCHIATRIC INPATIENTS:

Table 3.10 indicates a trend towards increased use of antidepressants; for example, 36% of patients were given antidepressants in 1980, compared with 45% in 1981. This trend becomes more significant when adjustment is made for the effect of age and sex differences between the years.

TABLE 3.10

Use of antidepressants in 1980 and 1981

Year	Treatment		Total
	no anti-depressants	given anti-depressants	
1980	163	95	258
1981	144	118	262
Total:	307	213	520

$X^2 = 3.63$ df = 1; corrected $X^2 = 3.9$*; $p < 0.05$.

Diagnostic practice over the period was examined. Table 3.11 indicates a trend towards increased diagnosis of biological depression. For example, 23% were diagnosed as biologically depressed in 1980, compared with 30% in 1981. This cannot be attributed to change in the age and sex composition of the cases between 1980 and 1981, as the effects of these acted in the opposite direction. The trend reaches significance when corrected for age and sex.

A RETROSPECTIVE STUDY OF THE IMPACT OF THE INTRODUCTION OF THE DST ON THE DIAGNOSIS AND MANAGEMENT OF PSYCHIATRIC INPATIENTS:

TABLE 3.11

Diagnosis of biological depression

in 1980 and 1981

Year	Diagnosis		Total
	biological depression (a + b)	all other diagnoses (c + d)	
1980	61	197	258
1981	80	182	262
Total:	141	379	520

$X^2 = 3.12$ df = 1; corrected $X^2 = 4.4^*$; $p < 0.05$.

(c) Treatment and diagnosis after the introduction of the DST.

Diagnostic and treatment practice was further investigated in the 1981 period after the introduction of the DST. During this period 162 patients, 62%, were given the DST. The first question addressed was whether there was an association between DST result and treatment with antidepressants in the patients under study. Table 3.12 indicates no association between the result of the DST and treatment with antidepressants.

A RETROSPECTIVE STUDY OF THE IMPACT OF THE INTRODUCTION OF THE DST ON THE DIAGNOSIS AND MANAGEMENT OF PSYCHIATRIC INPATIENTS:

TABLE 3.12

DST results and treatment with antidepressants

DST result	Treatment		Total
	not given anti-depressants	given anti-depressants	
DST negative	40	44	84
DST positive	33	45	78
Total:	73	89	162

$X^2 = .46$ df = 1; corrected $X^2 = .94$; n.s.

Any association between DST results and diagnosis was examined. Table 3.13 reveals there was a significant association between a positive DST result and the diagnosis of biological depression. Forty-five per cent of patients with positive DST results had a diagnosis of biological depression and 69% with negative DST results had other diagnoses.

TABLE 3.13

DST results and diagnosis of biological depression

DST result	Diagnosis		Total
	biological depression (a + b)	all other diagnoses (c + d)	
DST negative	26	58	84
DST positive	35	43	78
Total:	61	101	162

$X^2 = 3.3$ df = 1; corrected $X^2 = 5.7$*; $p < 0.05$.

A RETROSPECTIVE STUDY OF THE IMPACT OF THE INTRODUCTION OF THE DST ON THE DIAGNOSIS AND MANAGEMENT OF PSYCHIATRIC INPATIENTS:

The association between requesting a DST and treatment and diagnosis was next considered. Table 3.14 shows a strong association between requesting the test and treatment.

TABLE 3.14

Requesting DST, or not requesting DST and treatment

DST	Antidepressant drug		Total
	Not given	Given	
Not done	71	29	100
Done	73	89	162
Total:	144	118	262

$X^2 = 16.8^*$ df = 1; p <0.001.

Even when those with positive DST results were excluded, as shown in Table 3.15, this strong association remained. This association was only a little weakened by adjustment for age and sex. The data show that 29% of those who did not have the DST performed had a course of antidepressants, while 52% of those who had the test performed but who had a negative result were given antidepressants. There is a significant association, then, between requesting the DST and treatment with antidepressants, even when one excludes those with

positive DST results and looks only at the group on whom the DST was performed and had negative results.

TABLE 3.15

DST negative results and DST not requested associated with treatment

DST	Antidepressant drug		Total
	Not given	Given	
Not done	71	29	100
Negative	40	44	84
Total	111	73	184

$X^2 = 10.4^*$ df = 1; corrected $X^2 = 7.1^*$; $p < 0.01$.

Any association between ordering the DST and the diagnosis of biological depression was considered. Nineteen per cent of those who did not have the test performed were given the diagnosis of biological depression, while 38% of those who had the test were given that diagnosis. However, part of this association may be attributable to the significant association between a positive DST result and the diagnosis of biological depression. When those with positive DST results were excluded, as shown in Table 3.16, there was no association between ordering the test and the diagnosis of biological depression.

A RETROSPECTIVE STUDY OF THE IMPACT OF THE INTRODUCTION OF THE DST ON THE DIAGNOSIS AND MANAGEMENT OF PSYCHIATRIC INPATIENTS:

TABLE 3.16

DST negative results and DST not requested associated with diagnosis

	Biological depression		Total
	diagnosis not made	diagnosis made	
Not done	81	19	100
Negative	58	26	84
Total:	139	45	184

$X^2 = 3.5$ df = 1; corrected $X^2 = 1.6$; n.s.

In summary, the findings from the retrospective case-note study were as follows:

1. There was a significant trend towards increased antidepressant usage over the two periods under study.
2. There was a significant trend towards increased diagnosis of biological depression over the periods under study.
3. There was no association between DST results and treatment with antidepressants.
4. There was a significant association between DST results and diagnosis of biological depression.

A RETROSPECTIVE STUDY OF THE IMPACT OF THE INTRODUCTION OF THE DST ON THE DIAGNOSIS AND MANAGEMENT OF PSYCHIATRIC INPATIENTS:

5. There was a significant association between requesting the DST and antidepressant treatment.

5. Comment.

These findings were surprising. Changes in case mix between the years under study, with more women and an older population admitted in 1980 compared with 1981, might suggest that there should have been a greater proportion of cases of biological depression in 1980. Just the opposite was observed, with significant trends towards diagnosis of biological depression and treatment with antidepressants in the 1981 period. Are there plausible explanations which could relate these observations and the other findings of the study to the introduction of the DST?

Consider a typical career of a patient admitted to the unit. From clinical experience, on admission, decisions with regard to the ordering of the DST and to antidepressant treatment are made very nearly simultaneously. The patient is given the DST and often, antidepressants may be started at the same time. Some days later the DST result appears. It is my experience that once antidepressant medication has begun, decisions to stop it on the basis of the DST result are rare. That this should be so is, of course, quite understandable in terms of the

DST's 50% sensitivity for melancholia. Unfortunately, data to test this hypothesis - that is, data regarding changes in medication at the time the DST result became available - were not collected in this study.

On discharge, the diagnosis made by the psychiatric registrar takes into account the DST result. Thus, it could be argued, comes about the association between final diagnosis and DST result. The discharge diagnosis may also be influenced by the course of management, viz. antidepressants, and, in turn, this course of management is associated with the decision to perform the DST.

Thus a possible explanatory model exists. Why the requesting of the DST should be associated strongly with antidepressant treatment is unclear. Whether the psychiatrist's "set" with respect to the nature of depressive illness is altered by the development of specific laboratory tests for psychiatric disorders is one conjecture. As has been commented upon in Chapter One (p.25), Mellergard and Leroy have demonstrated the tendency of clinicians to give an effective treatment, antidepressant medication, a trial, even when the information base does not completely support a diagnosis of endogenous depression. In other words, when a simple, safe and effective treatment is available for a potentially lethal condition, the clinician may tend to over-diagnose the condition. When the rationale behind

a biological treatment for a psychiatric disorder is strengthened by the development of a biological test for the disorder, then that treatment might be over-prescribed, particularly if the biological test is only moderately sensitive.

Mantel and Haenszel[4] state: "The findings of a retrospective study are necessarily in the form of statements about associations between diseases and factors, rather than about cause and effect relationships". Thus it cannot be claimed that the increased use of diagnostic terms implying biological depression and the increase in use of somatic antidepressant treatment observed in the study was caused by the introduction of the DST. Neither can it be said that the requesting of the DST was causal in the decision to prescribe antidepressants. A controlled prospective study could perhaps address these issues. However, given that the associations discovered in the retrospective study might be known to the unit to be prospectively studied, then obvious difficulties arise. The process of future clinical judgment would no doubt be influenced by the discovery of associations between the introduction of the DST and changes in diagnosis and treatment.

While the DST may rally belief in an organic basis of some sorts of depression, it is puzzling that 42% of patients with positive DST results did not receive a

trial of antidepressants. Three factors may explain this finding. Firstly, there may have been a number of patients who were given the DST before a complete history had revealed medical conditions or drugs which may have invalidated the results. Secondly, the DST may not be as specific for biological depression as has been assumed (see p. 45). Thirdly, it may be that, as has been commented upon in Chapter One (p. 19), the correlation between treatment and diagnosis is not high in psychiatry.

Whether more notice should be taken of the DST result is another question, one which could, of course, be only answered by an outcome study.

No conclusions regarding causality of the observed change in diagnostic and treatment patterns can be drawn from this retrospective study. Factors other than the introduction of the DST may have affected diagnosis and treatment. Such factors include changes in admission policy, changes in patient management philosophy, and changes in the teaching curriculum of psychiatric registrars. While there were no known explicit policy decisions made regarding changes in these areas in the period of the study, it is possible that such changes did occur. It is also possible that the changes in management and treatment observed would have occurred without the introduction of the DST into the ward, as staff members became familiar with the literature surrounding the DST. Such variables were not, of course, controlled for, and as such they reflect a weakness of the study.

A RETROSPECTIVE STUDY OF THE IMPACT OF THE INTRODUCTION OF THE DST ON THE DIAGNOSIS AND MANAGEMENT OF PSYCHIATRIC INPATIENTS:

Any retrospective study, of course, has methodological problems relating to the biases of the study setting and the question of the representative nature of the cases and controls under study. In this study, we elected not to match patients before and after the introduction of the DST for variables such as age or sex. Instead, we elected to use the summary relative risk formula statistical technique of Mantel and Haenszel to control for such factors in our analysis of the data. However, in any retrospective study an internal examination of the data raises questions regarding the representative nature of the data, questions which cannot be completely satisfied by an internal analysis alone. As such, any associations demonstrated in the study should be treated cautiously.

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CHAPTER TWO

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