HYPOTHALAMIC-PITUITARY-ADRENAL AXIS FUNCTION AND HYPOTHALAMIC-PITUITARY-THYROID AXIS FUNCTION IN MENTALLY RETARDED PATIENTS WITH AND WITHOUT SELF-INJURIOUS AND/OR AGGRESSIVE BEHAVIOUR

by

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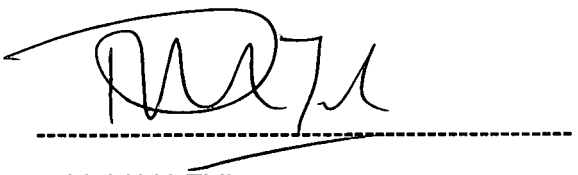
DECLARATION

I hereby declare that the work that is submitted here is the result of my own independent investigation. Where help was sought, it was acknowledged. I further declare that this work is submitted for the first time at this university/faculty towards an M. Med. Sc. degree (Clin.Pharm.) and that it has never been submitted to any other university/faculty for the purpose of obtaining a degree.



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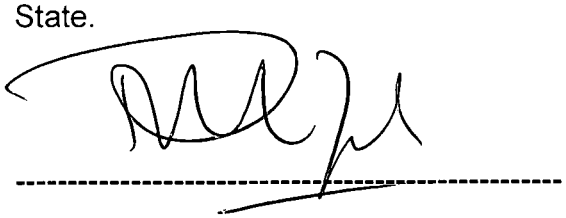

P.M. VAN ZYL

30/3/2004

Date

DEDICATION

Dedicated to Gert

For educating me in the art of perseverance.

"Ek ken 'n plek
Waar daar kinders woon
wat lank, lank t'rug
geëet het van die ander boom se vrug
Nou bly hul leef- vir ewig kind
Ongeraak deur goed en kwaad
Onskuldig aan die stryd
om die een soos die ander te laat lyk"

Paulina van Zyl
"Twee bome"
Kosmos
c. 1999

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LIST OF ACRONYMS

ACTH:	Adrenocorticotrophic hormone
BAMs:	Behaviour altering medications
CI:	Confidence interval
CRF:	Corticotropin-releasing factor also known as Corticotropin-releasing hormone (CRH)
CSF:	Cerebro spinal fluid
D1:	Dopamine 1 receptors
D2:	Dopamine 2 receptors
DST:	Dexamethasone suppression test
EPS:	Extra pyramidal syndrome
GABA:	Gamma amino butyric acid
GR:	Glucocorticoid receptors
5HT:	5-Hydroxy tryptamine, also known as serotonin
HHH:	Hypothalamic-hypophysiotrophic hormone
HIAA:	Hydroxy-indole acetic acid
HPA:	Hypothalamic-pituitary-adrenal
HPT:	Hypothalamic-pituitary-thyroid
IQ:	Intelligence quotient
LSS:	Low serotonin syndrome
OCD:	Obsessive compulsive disorder
PIF:	Prolactin inhibiting factor
SAT:	Symptomless auto-immune thyroiditis
SIB:	Self-injuring behaviour
SRIF:	Somatrophin release inhibiting factor also known as Somatostatin or growth hormone releasing inhibiting factor.
SSRIs:	Selective serotonin re-uptake inhibitors
T3:	Triiodothyronine
T4:	Thyroxine
TRH:	Thyroid-releasing hormone
TRHST:	Thyroid-releasing hormone stimulation test
TSH:	Thyroid-stimulating hormone (also known as thyrotrophin)

CHAPTER 1
GENERAL PERSPECTIVE AND ORIENTATION

1.1 INTRODUCTION

Aggressive and self-injuring behaviour plays an important part in the every-day lives of many institutionalised mentally retarded persons. Within the context of a growing trend of de-institutionalisation, it remains a prominent factor determining both a person's suitability for community placement and contributing to the eventual success or failure of such a placement. Lakin, Hill, Hauber, Bruininks and Heal (1983:15) reported maladaptive behaviour to be the major cause for admission or readmission to institutions; aggressive and disruptive behaviour contributing the major component. In addition, institutionalisation may also be the trigger for particularly self-injurious behaviour (Winschel & Stanley, 1991: 307).

It follows that institutions for the mentally retarded are and will increasingly become areas of concentration of mentally retarded persons with behaviour problems. Institutions for mentally retarded persons have the obligation to provide a safe environment to a very vulnerable population. Aggressive and self-injuring patients may cause problems in terms of the organisation of activities and services; it has financial implications, while ethical issues have to be considered in policies guiding the management of the problem. For the affected individual it affects his/her socialisation and participation in activities. It may cause other residents and staff injuries and fear, resulting from the fact that they live under "a reign of terror". The conduct of staff members are also often under scrutiny in these instances and there is a degree of professional vulnerability that is created when a staff member has to protect him-/herself or others or establish control within the limitations set by professional conduct.

1.2 PROBLEM STATEMENT

The clinician dealing with a mentally retarded person with aggression and self-injurious behaviour are confronted by several diagnostic dilemmas. Physical causes of the behaviour must be excluded. These may be very subtle and difficult to elicit in low-functioning individuals. Then it should be determined whether the behaviour is caused by an underlying psychiatric condition. The fact that the diagnostic process in psychiatry relies heavily on interpersonal interaction and the patient's ability to express subjective experiences makes this a daunting task in a mentally retarded person. This is especially true in persons with an IQ of less than 50. This population has an increased impairment of communication; there is distortion of the usual symptomatology of defined psychiatric syndromes; and it is difficult to elicit emotional symptoms. Some behaviour patterns, like head–banging, are unique to mentally retarded persons. The recognized tools for assessment of psychiatric patients, namely the DSM IV and ICD 10 were developed for persons with a normal IQ.

Being unable to establish a definitive diagnosis, the selection of appropriate therapy is also at risk. It is understandable that the widely used practice of prescribing non-selective typical antipsychotics is continuing despite a growing antipathy against the use of these drugs. Other alternatives exist, yet there is very little indication as to which drug to use for which patient. The problems of a trial-and-error method of drug selection are confounded by the problems regarding the monitoring of drug response. The response time lag of the medication; the fluctuating nature of symptoms in a large number of cases; and the patient's non-participation in the evaluation process are factors that contribute to the scenario.

The importance of making the correct drug selection as early as possible is underlined by the fact that failure of treatment may be marked by a major incident, resulting in serious injury or disability.

1.3 CONCEPTUALIZATION

Behaviour represents the interaction of an individual with his physical and social environment. Aggression is a specific adaptive behaviour, an expression of the integration of both biological and environmental stimuli, molded into a response intended to ensure the survival of the individual in hostile conditions. Aggression is necessary and justified in certain situations, but it should always be under control to ensure appropriate expression. It is this control element, effected by the ability to learn and adapt to social rules, which is unique to human aggression (Ramirez, 2002:3)

Searching for the origins of uncontrolled or inappropriate aggression, one has to consider the events following exposure to a potential threat (that can also be called a stressor, or noxious stimulus) The central nervous system has to assess the relevance of the threat or stressor and control the responses of the body in various organs, to mobilize the organism as a whole (Haller, Makara & Kruk, 1998:85). The hypothalamic-pituitary system plays a pivotal role in adaptation to hostile conditions. It is now well established that corticotropin releasing factor (CRF) is responsible for mediating the effect of stressors on the hypothalamic-pituitary-adrenal axis (Carrasco & Van de Kar, 2003:236), as well as the control of the behavioural, endocrine, autonomic and immunological responses to stress. CRF–containing neurons are widely distributed in the brain, with the highest density in the hypothalamic paraventricular nucleus. The CRF neurons control the release of adrenocorticotropin (ACTH) from the pituitary. ACTH, in turn, regulates the production of cortisol by the adrenal gland. CRF neurons also have extensive interactions with both serotonergic and noradrenergic systems (Nemeroff, 2002:13-14). The hypothalamic paraventricular nucleus additionally plays a role in the secretion of the stress-induced release of ACTH, oxytocin, prolactin and renin. Other hormones involved in the stress response include vasopressin, also involved in the activation of the HPA axis; vasoactive intestinal polypeptide; responsible for sustained effects of the stress response; neuropeptide Y is responsible for homeostatic responses; while substance P has an anti-anxiogenic effect (Carrasco & Van de Kar, 2003:256). The

neurotransmitters serotonin and noradrenaline also play an important part in the stress response.

In the case of a mentally retarded person, the neuro-chemical processes occur against an abnormal neurological background and interaction is limited and altered by physical and communicative limitations. The expression is therefore distorted by the anatomical aberrations and may not reflect the original neuro-chemical process as expected in a normal person. It may therefore also not be possible to distinguish between different underlying neuro-chemical processes by interpreting behaviour patterns in this population. It is, for instance, a well-known phenomenon that depression in adolescents and children often manifests in the form of behaviour problems and aggression. It is also backed by evidence that depression contributes to a dual diagnosis in mentally retarded patients. In a study of 320 people with learning disability, increasing severity of behaviour problems was associated with increased prevalence of psychiatric symptoms. Depression showed the most marked association and anxiety symptoms were associated with self–injuring behaviour (Moss, Emerson, Kiernan, Turner, Hatton & Alborz, 2000:455).

The measurement of internal hormonal responses provided an important window on neurotransmitter processes in vivo in depression research. Cortisol hypersecretion has been the most consistent biological marker in depression and it is seen as a marker for endogenous depression. An increase in adreno-corticotrophic hormone (ACTH) secretion with a secondary increase in cortisol and a loss of normal circadian variation is seen in 60 % of depressed patients, reflected in a blunted response to the dexamethasone suppression test as adapted by Carroll (1982:294). This test has been used extensively in depressed patients to evaluate the hypothalamic-pituitary-adrenal axis.

The involvement of the hypothalamic-pituitary-thyroid (HPT) axis in depression is demonstrated by the co-morbidity of hypothyroidism and depression, the demonstration of HPT dysfunction in depressed patients, and

the application of hormones of the thyroid axis in the treatment of depression (Nemeroff, 1989:16).

The thyroid-releasing hormone (TRH) stimulation test is the standard method to assess the hypothalamic-pituitary-thyroid (HPT) axis. Subclinical hypothyroidism (increased release of thyroid-stimulating hormone (TSH) in response to thyroid-releasing hormone in the presence of normal levels of T3 and T4) is more common in patients with bipolar mood disorder. A quarter of patients with unipolar depression have a low output of TSH and a blunted response to TRH representing a subclinical hyperthyroidism. The test has been widely applied in depressed patients, but no reference to its use in mentally retarded patients could be found so far.

1.4 RESEARCH GOAL AND OBJECTIVES

The goal is to compare hypothalamic-pituitary-adrenal axis function and hypothalamic-pituitary-thyroid axis function in mentally retarded patients with and without self-injuring and aggressive behaviour at the Kosmos Centre, Free State Psychiatric Complex, through the application of the dexamethasone suppression test and the thyroid-releasing hormone stimulation test.

The objectives are as follows:
In the first place it will be a literature study covering the following topics:

- Self-injurious and aggressive behaviour and the theories regarding the underlying neurotransmitter action.
- The hypothalamic-pituitary-adrenal axis and dexamethasone suppression test.
- The hypothalamic-pituitary-thyroid axis and the thyroid-releasing hormone stimulation test.
- Ethical considerations in research on mentally retarded persons.

In the second place will follow the neuro-endocrine assessment of test subjects.

1.5 RESEARCH APPROACH AND METHODOLOGY

The study was designed as a matched control study to evaluate the difference in neuro-endocrine responses in subjects with the above-mentioned behaviour and those without it.

A preliminary selection of subjects was first made from a database that was compiled from the clinical notes of patients. A final selection was made after a screening process involving a physical examination and discussing the subject with the ward personnel. Individual consent was obtained from the relevant guardians.

The neuro-endocrine assessment involved the thyroid-releasing hormone stimulation test (TRHST) and the dexamethasone suppression test (DST), as well as baseline levels of T4, prolactin and cortisol.

A pilot study was undertaken to assess the practical aspects of the TRHST. Two patients not included in the study population were involved. Particular aspects that were assessed were the number of patients that could be evaluated in one session and the degree to which patient co-operation would be possible.

1.6 ARRANGEMENT OF THE DISSERTATION

The present chapter introduces the subject of aggression and self-injurious behaviour with specific reference to its relevance to institutions; the problematic nature of diagnosis is discussed, followed by an exploration of hormonal stress-adaptation and the application of these processes as biological markers. The broad goal and objectives of the study are outlined as well as research approach and methodology.

In the next four chapters the literature that was studied, is described.

Chapter 2 deals with the issues of self-injurious and aggressive behaviour in mentally retarded persons, describing the extent, definition and context in which it occurs as well as an overview of both historical and current management trends.

In chapter 3, biochemical models of neurotransmitter involvement in aggression and self-injury are discussed.

Chapter 4 focuses on the role and functions of the hypothalamic–pituitary-adrenal axis and the hypothalamic-pituitary-thyroid axis as well as the dexamethasone suppression test and the thyroid-releasing hormone stimulation test that is used to measure these functions.

Ethical considerations regarding research in mentally retarded persons, including unresolved challenges, are discussed in chapter 5.

Chapter 6 describes the methodology that was followed, describing the study environment and demarcating the study population as well as describing the assessment methods.

Chapter 7 deals with the results of the study and the statistical analysis of the results.

Chapter 8 comprises a discussion and recommendations regarding the findings of the study.

1.7 CONCLUSION

The study investigates the phenomenon of aggression and self-injurious behaviour in mentally retardates within the framework of the biological adaptation functions of the hypothalamic-pituitary-adrenal axis and the hypothalamic-pituitary-thyroid axis with the view to explore the utilisation of the measurement of these functions as biological markers.

Bearing these perspectives in mind, the problematic nature of aggressive and self-injuring behaviour in institutionalised mentally retarded persons will be explored and described in Chapter 2.

CHAPTER 2
SELF-INJURIOUS AND AGGRESSIVE BEHAVIOUR IN MENTALLY RETARDED PERSONS

2.1 INTRODUCTION

As the most dramatic expressions of problem behaviour in mentally retarded persons, self-injury and aggression are challenging mental health systems, mental institutions, caretakers and health care workers to provide adequate solutions, ensuring a safe and congenial environment for optimal development of the limited ability of mental retardates.

2.2 EXTENT OF THE PROBLEM

In a total population study in two areas of England to identify the situation and characteristics of people reported to exhibit challenging behaviours, Emerson, Kiernan, Alborz, Reeves, Mason, Swarbrick, Mason and Hatton (2001:92) reported a prevalence of challenging behaviours of 15 % of people with mental retardation who are in contact with education, health or social care services for people with mental retardation. The presence of aggression was reported in 7 %, destructive behaviour in 4 %, and self-injury in 4 %. Challenging behaviour occurred more in males, adolescents and young people. Persons with more demanding challenging behaviour were more likely to be dependent in terms of self-care and had less communicative ability.

Behaviour problems such as aggression, self-injurious behaviour, tantrums, property destruction, stereotypes, pica and rumination are exhibited by 30-55 % of institutionalised persons with mental retardation (Baumeister, Todd & Sevin, 1993:281).

2.3 DEFINITION AND CONTEXT OF SELF-INJURIOUS AND AGGRESSIVE BEHAVIOUR

Aggression is not unique to mental retardation, nor is it that all mental retarded persons are aggressive. The lack of control of aggression by cognitive function may, however, cause inappropriate expression of anger in vulnerable individuals.

2.3.1 Self-injurious behaviour

Self-injuring behaviour can be seen as self-directed aggression. It is defined as acts that result in physical injury to a person's own body and are usually repetitive, rhythmic and likely to produce pain in the absence of sensory impairment (Baumeister *et al.*,1993:275).

Self-injurious behaviour is highest in persons with profound mental retardation. Approximately 10 – 20 % of persons living in institutions for the developmentally disabled evince self-injurious behaviour. It is normally characterised by biting oneself, hitting oneself, or banging one's head. Self-injurious behaviour is positively correlated with other forms of aberrant behaviour such as stereotypy and aggression (Baumeister *et al.*,1993:275).

The context in which self-injurious behaviour occurs includes prisons, corrective institutions for adolescent offenders, inpatient facilities for the mentally retarded as well as inpatient adolescent psychiatric units. In each of these contexts some individuals are described who have no history of self-injurious behaviour prior to admission. This observation is also consistent with observations in animals (Winschel & Stanley, 1991:307).

2.3.2 Aggression

Aggression represents one of the most serious behaviour problems in persons with mental retardation. It has been estimated that approximately 30 – 55 % of persons in state institutions for the developmentally disabled, display physical aggression (Baumeister *et al.,* 1993:281). Aggression is the primary reason that individuals are admitted or re-admitted to institutional settings and appears to be the primary reason why persons with mental retardation are placed on psychotropic/behaviour control medication (Baumeister *et al.*, 1993:281).

Like self-injury, aggression and destructive behaviour positively correlate with the degree of cognitive deficit. Males are more likely to exhibit these challenging behaviours than females.

2.3.3 Dual diagnosis

The term dual diagnosis for the co-existence of mental retardation and mental illness became popular during the 1970's. The prevalence of mental disorders is higher among people with mental retardation than in the general population. Rates reported in the literature vary considerably, ranging from 10-80 % (Borthwick-Duffy, 1994:17). Problem behaviour may be exhibited as a manifestation of a psychiatric disorder in mentally retarded persons (Borthwick-Duffy, 1994:24).

The lifetime prevalence of psychotic disorders in people with learning disabilities is about five times that of the general population. Moss *et al.* (2000:454) demonstrated that the overall prevalence of psychiatric disorders in people with more demanding challenging behaviour was over twice the prevalence compared to those who had no challenging behaviour. Depression was four times as prevalent among those whose challenging behaviour was more demanding than in people showing no challenging behaviour, while hypermania was three times as prevalent (Moss *et al.*,

2000:454). Linaker (1994:66) found that psychiatric disturbances and other behaviour disturbances were more common among assaultive mentally retarded persons in an institutionalised setting. Physical aggression may thus be a manifestation of a psychiatric disorder, like schizophrenia or depression. It may also be a manifestation of anxiety or fear. In the majority of cases in an institutional setting, it is environmentally reactive (Bongiorno, 1996:1145).
Researchers investigating psychiatric referrals in a community-based programme for the mentally retarded in Nebraska in the late seventies found 114 patients of the 798 retardates in the population referred for a psychiatric assessment over a three-year-and-five month period to have both mental retardation as well as a psychiatric disorder, representing 14.3 % of the mentally retarded population in the program. An organic brain syndrome with a behavioural reaction was diagnosed in 18.4 % of the subjects. The diagnosis of organic brain syndrome with behavioural reaction was used for those patients exhibiting inappropriate acting out (e.g. emotional lability, impulsivity, poor judgement in social situations and frequent tantrums) without psychosis (Eaton & Menolascino, 1982:1298). They also diagnosed adjustment reactions in 21 % (24) of the sample.

Eaton and Menolascino (1982:1298) attribute their findings to a combination of an organic predisposition to overact on stimuli and the limited understanding of social interactions by the subjects. The reasons for the increased risk for psychiatric illness are probably because of interaction among several factors. Firstly there is the possibility of underlying structural or functional damage of the brain, which may itself present both as cognitive impairment and a psychiatric disorder. Psychological stress caused by associated disabilities such as epilepsy or cerebral palsy may make the individual more susceptible to both psychiatric disorder and problem behaviour. Physical factors such as an acute illness or thyroid dysfunction often presents as an emotional or behaviour disorder.

The role of the social and physical environment should also not be underestimated. Mentally retarded persons have less control over their lives and institutionalised individuals are prone to bereavement caused by staff

changes. Lack of communication skills may compound emotional problems. In higher functioning individuals the social consequences of their disability, such as difficulty in finding employment, may contribute to low self-esteem and ultimately in psychiatric disorder. Epilepsy may complicate this situation further. A much increased risk for developing Alzheimer's disease is specifically associated with patients with Down's syndrome.

The diagnosis of mental illness in people with mental retardation can be difficult, especially when the diagnosis is dependent on the communicative ability of the patient, like in schizophrenia (Wright, 1982:499; Reid, 1972:211). Depending on the degree of disability, mentally retarded persons may well have the ability to articulate feelings and emotions, yet interpretation may still be difficult. Symptoms like insomnia and diurnal variation are also affected by the use of various drugs that are extensively used in mentally retarded patients (Wright, 1982:499). Diagnosis in low functioning individuals relies heavily on long-term observation of the individual by observers who know the person well (Reid, 1972:207). Recognition demands that the observer (s) should know the person well, be in touch with mainstream psychiatry, and is adversely affected by a high workload (Reid, 1972:211).

Persons with more severe mental retardation and more limited communication may not be able to communicate their emotions and feelings at all. Here, the role of the caretaker with a long-term exposure to the individual is crucial. Mood disorders may be distinguishable by a history of changes in sleep pattern, appetite, moods, self-help skills and sociability. The increased risk of self-harm associated with depression may manifest as severe self-injury in a mentally retarded person. Self-injury, aggression, screaming, crying, stereotypes and temper tantrums may well function as depressive equivalents in mentally retarded persons. Meins (1995:42) found that in patients with a more severe degree of mental retardation, depression was often expressed by psychomotor agitation and irritable mood, rather than depressed mood and reduced energy or fatigue.

Persons with mental retardation may, however, also develop problem behaviour in the absence of psychiatric illness. Environmental and social factors do play an important role here. The behaviour may be the result of boredom, or as a mechanism to attract attention from caretakers. It may also be an attempt to communicate negative emotions or physical discomfort. Age, IQ and gender have been identified as factors that are associated with challenging behaviour. The prevalence of challenging behaviour increases with age during childhood, reaching a peak at 15–34 years and then starts declining (Borthwick-Duffy, 1994:23).

2.4 THE MANAGEMENT OF SELF-INJURIOUS AND AGGRESSIVE BEHAVIOUR

Various schools of thought shaped the management of self-injurious and aggressive behaviour through the years. Currently a multidisciplinary team approach is favoured, with prominent roles for both psychopharmacology and psychotherapy, after the exclusion of physical causes.

2.4.1 Historical overview of management trends

In 1801 Dr. Jean Itard published *De Education D'un Homme Savage* in which he described the re-education of a youth that was found running in the woods. He expressed the view that mental deficiency could be cured by special methods of education. A pupil of Itard, Eduard Seguin, also believed that mental deficiency could be cured by special education and *Idiocy and its treatment by the Physiological Method* was published. Seguin eventually settled in America, where his teachings influenced educational systems to a large extent. The well-known Montessori method is based on his teachings.

In general, however, there was little interest in the problem of mental deficiency during the 19th century, until two Frenchmen, Binet and Simon,

developed their Intelligence Tests between 1905 and 1908. They introduced the concept of mental age as opposed to chronological age. These initial tests had many flaws, but were modified a few years later by Terman. This modification was known as the Stanford modification. Terman introduced the concept of intelligence quotient (IQ).

At about the same time that the Binet Simon Test was invented, Clifford Beers published his work *The Mind that found Itself.* This book stimulated public interest in so-called "mental hygiene". "Mental hygiene, besides trying to secure the right conditions for the development of the average person, is concerned with discriminating these special types and with procuring for them suitable training and environment". The book introduced this new field, describing testing, as well as the influence of heredity and statistics underlying social problems. The provision of homes for the "socially mischievous", farm colonies, industrial training and special schools is also described. During 1912, Beers's writings became popular in South Africa and sparked the development of homes and institutions for the mentally retarded through the formation of a committee that investigated the situation, collected funds and made provision for the institutions for the mentally retarded. In 1916 Act No. 38 was passed which made provision for the certification, care and supervision of mental defectives and mentally disordered (Minde, 1975:1717).

The early developments in the management of the mentally retarded thus centred on habilitation and education, rather than treatment. The absence of psychiatrists in this field during these early years is explained by the introduction of psychoanalysis in the United States by Brill in 1908. This model did not accommodate mental retardation and psychiatrists became alienated from the question of mental retardation. The period from 1900 until 1960 became known as the "tragic period".

When the first era of psychopharmacology dawned in 1952 with the use of chlorpromazine, the make-up of multidisciplinary teams responsible for the care of mentally retarded patients was thus not able to apply the new advances to the mentally retarded. It was only in the period between 1960 and

1970 that Menolascino introduced the concept of "dual diagnosis", also known as the "other" dual diagnosis to distinguish it from the dual diagnosis of mental illness and substance abuse.

In 1937 Bradley introduced dextroamphethamine for calming hyperexcitable-hyperactive children (Ban, 2001:712).

The first "psychotropic drugs", referring to all drugs with an effect on mental activity and human behaviour, were introduced within the eight years from 1949 to 1957. The set of six drugs consisted of two neuroleptics chlorpromazine and reserpine, two antidepressants iproniazid (a monoamine oxidase inhibitor) and imipramine, an anxiolytic, meprobamate, and a mood stabiliser, lithium carbonate. The introduction of these therapeutically effective drugs and the development of the spectrophotofluorimeter in the mid-1950s led to the development of neuropsychopharmacology. The spectrophotofluorimeter could measure the concentration of cerebral monoamines and their metabolites (Ban, 2001:714).

The beginning of the 1970s marked a movement towards adaptive training for mentally retardates. A group of patients, however, still remain who cannot benefit from this approach, because of their adverse behaviour rather than by their IQ score.

Eaton and Menolascino (1982:1302) praise the benefits of community care which were popularised during the 1970s in regard of the prevention of the development of the syndrome of detachment in mentally retarded patients. Patients are allowed closer contact with their families; maintain close relationships with caretakers; and live in homelike settings and in normal communities. These community placements were made possible by the advances in medical and psychiatric treatment, which negated the need for institutional methods to control problem behaviour. These methods included isolation rooms, physical restraints and excessive neuropharmacological interventions. Other positive results of improved medical and psychiatric care include increasing the morale and confidence of persons working with

mentally retarded persons, with more comprehensive training programmes for the mentally retarded being implemented.

2.4.2 The role of psychotherapy

Within the realm of psychotherapy there are also different approaches to the problem of self-injuring behaviour and aggression.

2.4.2.1 *Behaviour modification*

The environmental contingencies in which self-injurious behaviour occurs among mentally retarded persons have been investigated extensively. A variety of conditioning techniques have been devised to diminish self-injurious behaviour. Two broad categories of factors responsible for the maintenance of behaviour problems are distinguished, namely escape behaviour, controlled by negative reinforcement processes, and attention-seeking behaviour, controlled by positive reinforcement processes.

Behavioural techniques developed to deal with self-injurious behaviour include the teaching of communication skills, extinction, sensory extinction, punishment, alternative sensory activities, timeout and overcorrection.

2.4.2.2 *Positive behaviour support*

"In positive behaviour support the emphasis is on relationship and instruction, rather than consequence and punishment" (Bongiorno, 1996:1144). As most acts of aggression are environmentally reactive, each individual act should be analysed in regard of its origin, response perpetrator and victim. It should never be assumed to be unprovoked and due to excessive dopamine action that can only be treated by antipsychotic medication. It can also be due to

stimulation of beta-adrenergic receptors in a flight reaction or alpha-receptors during a typical attack mode.

Pyles, Muniz, Cade and Silva (1997:186) contrast the conditions of research settings and clinical settings with regard to infrastructure for successful behavioural interventions. Therapists in research settings are highly trained, while direct care staff usually have high school training. In research settings there are high ratios of staff:participants, that cannot be compared to staff:patient ratios in clinical situations. In addition, the researcher is usually dedicated to a specific patient for a specific timeslot, while caretakers are also responsible for other tasks besides direct patient contact.

According to Emerson and Emerson (1987:104,105), successful application of behaviour programmes relies on a chain of sufficient numbers of adequately trained staff, supported by expert behavioural consultants, consistently applying the selected techniques in an environment of access to constructive activities and with minimal competing behaviours of other residents.

It is therefore not surprising that applied settings cannot reproduce the success of psychotherapy interventions in research settings.

2.4.3 The role of psychopharmacology

A significant number of people with dual diagnosis are treated with psychotropic agents. Spreat and Conroy (1998:512) reported a 22 % use of neuroleptic drugs, 5.9 % antidepressant use and 9.3 % anxiolytic use in adults with mental retardation. Baumeister *et al.* (1993:274) reported a mean prevalence psychotropic drug use of 57 % in institutions, based on a literature survey. (This included the use of both anticonvulsants and neuroleptics.)

Many reasons for high psychotropic drug use exist. These include a lack of staff, lack of access to professionals, and lack of command of appropriate assessment techniques. However, these or any other reasons are not

sufficient to explain the large numbers of persons with mental retardation who take psychotropic medications. Pharmacological interventions have become some of the most widely used intervention techniques with persons evincing mental retardation despite the fact that many drugs are ineffective and suppress behaviour generally and cause a number of lasting deleterious side effects (Matson, Bamburg, Mayville, Pinkston, Bielecki, Kuhn, Smalls & Logan, 2000:265). Given the large discrepancy between the use of antipsychotic drugs and the actual diagnosis of psychotic conditions, it is likely that in most cases the medication is for sedation (Pyles *et al.,* 1997:188). Ratey and Gordon (1993:65) ascribe the positive effect of antipsychotics on aggression as "sedation and cognitive dulling' that may even have a detrimental effect on behaviour.

The problem with psychotropic drugs is that it is not selective for the problem behaviour (Baumeister *et al.*, 1993:275) and may cause serious, lasting and even life-threatening side effects. The drugs may also affect an individual's behaviour negatively and affect learning, skill acquisition and response to reinforcement (Pyles *et al.,* 1997:188). The use of neuroleptic drugs should therefore always take into account the possible risk:benefit ratio.

Pyles *et al.* (1997:193) identify four uses for so-called behaviour altering drugs (BAM's), namely for the treatment of a psychiatric illness; as A short-term crisis intervention for severe maladaptive behaviour; when medication is prescribed for a medical condition with secondary effects on behaviour (for example carbamazepine for an epileptic patient with secondary effects on mood); and the fourth (controversial) application is for the management of a behaviour that is not part of a psychiatric condition. This last application is only permissible as a temporary measure in cases that do not respond to adequate behavioural therapy intervention.

2.4.3.1 *Various groups of behaviour altering medication*

Antidepressants are used for, among other indications, the treatment of major depression. Selective serotonin re-uptake inhibitors (SSRIs) are the treatment of choice, due to their more favourable side effect profile. The serotonergic antidepressants are also effective in the treatment of obsessive compulsive disorder. The involvement of serotonergic systems in self-injury and aggression supports the SSRIs as possible therapeutic agents. Although various SSRIs have been found to be effective in challenging behaviour, it should nevertheless be used with caution in this population, as it may trigger a manic or hypomanic phase in bipolar states and fluoxetine has been found to cause aggravation of aggressive behaviour in mentally retarded persons (Antochi, Stravakaki & Emery, 2003:141). Aman, Collier-Crespin and Lindsay (2000:104) concluded that there were "enough positive data to justify cautious clinical trials of the serotonergic antidepressants in patients with self-injuring behaviour".

Benzodiazepines should only be used for short-term treatment in anxiety disorders, as they are associated with over-use, abuse, dependence and behavioural problems caused by the disinhibiting effects of the drugs (Ratey & Gordon, 1993:65).
Apart from anxiety disorders, buspirone has been shown to be effective in agitation and challenging behaviours without the side effects associated with the use of the benzodiazepines. There is no sedation and cognitive abilities are unaffected (Ratey, Sovner, Mikkelson & Chmielinski, 1989:384). Ratey and Gordon (1993:68) recommend the use of buspirone for patients with pre-menstrual aggression.

Craft, Ismail, Krishnamurti, Mattews, Regan, Seth and North (1987:687) report that lithium is effective in the treatment of both aggression and self-injuring behaviour in this population. They caution, however, that the risks of lithium therapy should be carefully weighed against the potential benefit and they recommend a two-month trial in patients with resistant aggressive or self-injuring behaviour, necessitating long-term hospitalisation.

According to the model explaining self-injury in Lesch–Nyhan syndrome, the dopaminergic system is implicated in self-injury. As such, a dopamine antagonist may well be justified. Haloperidol has been proven to be effective in the treatment of aggressive behaviour. It is the over-use of the older generation of antipsychotics, however, that is cause for concern. The potential of severe and lasting side effects, including neurolep malignant syndrome, extrapyramidal symptoms and tardive dyskinesia associated with the typical antipsychotics must be borne in mind in analysing the risk-benefit relationship.

The fact that the atypical antipsychotics offer a better side effect profile in terms of their tendency to cause extrapyramidal symptoms and tardive dyskinesia, led Cohen, Ihrig, Lott and Kerrick (1998:230) to explore the use of risperidone as a treatment for aggressive and self-injurious behaviour in adults with mental retardation. They reported a definitive reduction in the target behaviours with minor side effects in the small study of eight subjects. Randomised double-blind, placebo controlled studies with risperidone show a definitive improvement of disruptive behaviour, including aggression and self-injury, in children with a sub-average IQ (Aman, De Smedt, Derivan, Lyons, Findling & The Risperidone Disruptive Behaviour Study Group, 2002:1343) and adolescents with subaverage cognitive abilities (Buitelaar, Van Der Gaag, Cohen-Kettenis & Melman, 2001:246). Snyder, Turgay, Aman, Binder, Fisman and Carroll (2002: 1034) also reported an increase in prosocial behaviour.

The rationale for the use of olanzapine in the treatment of self-injurious behaviour was based on the findings of Breese *et al.* (1990:482) that the dopamine (D1) receptor was the most likely mediator of this kind of behaviour. Olanzapine has a higher affinity for the D1 receptor than other antipsychotics. McDonough, Hillery and Kennedy (2000:678) found positive results in a pilot study of seven intellectually disabled adults with self-injurious behaviour on olanzapine. Janowski, Barnhill and Davis (2003:1263) found olanzapine to be an effective treatment for aggression, self-injurious behaviour or destructive/disruptive behaviours in a group of 20 institutionalised intellectually

disabled patients with various psychiatric conditions. They found that when olanzapine is used as an adjunct therapy to typical antipsychotics, the dose of the typical antipsychotic could be decreased or the drug could even be stopped due to the improvement in behaviour.

The atypical antipsychotics in these studies were in general tolerated well, but side effects like weight gain, the possibility of epilepsy, secondary diabetes and its effect on triglycerides and cholesterol (Janowski *et al.*, 2003:1263) should be borne in mind.

Cohen, Fitzgerald, Okos, Khan and Khan (2003:62) investigated the use of ziprasidone, a weight neutral atypical antipsychotic, in 40 mentally retarded patients with maladaptive behaviours who suffered from excessive weight gain on other agents. The drug was found to be effective in maintaining control of maladaptive behaviour; the patients lost weight; and the lipid profile remained normal during the six month follow-up period.

Aman *et al.* (2000:103) conclude that antipsychotics are undoubtedly beneficial to some patients with severe self-injury, yet there is no way of predicting who the responders will be.

Controversy surrounds the issue of the efficacy of the opioid antagonist, naltrexone, in the treatment of self-injury. Aman *et al.* (2000:104) express the opinion that it is no more effective than antipsychotic drugs. A positive effect may not necessarily reflect the involvement of the opioid system, but may be due to a mild anxiolytic effect.

The beta-blockers propranolol and nadolol are used for the treatment of aggression and self-injury (Antochi *et al.*, 2003:142). Ratey and Gordon (1993:68) hypothesise that beta-blockers lower the level of arousal in patients with hyperarousal. Aman *et al.* (2000:104) recommend careful empirical trials in the clinical situation.

2.4.4 Integrating psychotherapy and psychopharmacology

A competitive rather than a co-operative spirit in different modalities hampers the integration of concurrent therapies. Parallel developments of modalities rooted in opposing views regarding the aetiology of mental illness (i.e. neurochemical vs. psychogenic), as well as the divergent goals of treatment underlie the gap between psychotherapy and pharmacotherapy. The inability to integrate the two modalities appears to be a persistent feature of the field of psychiatry. This trend is strengthened by rigid preoccupation within the different disciplines. Lack of resources within institutions to provide for a broad exposure to diverse modalities contributes to a deficient exposure and knowledge regarding available options.

Paramount in the search for the optimal combination and appropriate application of the two approaches lies the question of their individual efficacies and defined role in the clinical setting. The answer to this can only be established through research. Unfortunately, research in both fields are plagued by a number of obstacles.

Matson *et al.* (2000:284) reported major problems with regard to research on the efficacy of psychopharmacology. Research methods differed greatly and there is a lack of a standardised and reliable scale for self-injurious behaviour. Emergency intervention in severe cases may mask partial benefits. Failure to compile a homogenous group of research subjects is a common problem. Some studies also did not distinguish between self- and outward-directed aggression. Non-specific sedating effects and the presence of undiagnosed mood disorders complicate interpretation of beneficial effects. They (Matson *et al.*, 2000:292) conclude that although antipsychotics are extensively used in an attempt to control aggression and self-injurious behaviour, it is not clear that there is a sufficient benefit to justify the exposure to the morbid side effects of these drugs.

However, it is also true that an anti-research climate exists in drug therapy in this particular patient group, consisting of numerous ethical and regulatory

barriers, societal bias, lack of institutional and public endorsement, patient and staff co-operation, and an escalation of pressure for patients' rights. Perhaps the most debated issue is that of informed consent. Ironically, the groups of patients most likely in need of improved pharmacotherapeutic intervention are also those who are the least able to give informed consent.

Accounting for both pharmacological as well as psychosocial factors in the methodology, diagnosis and statistical analysis in research design and interpretation as well as the application of data derived from a heterogeneous research population to an individual patient in a general ward situation contribute to the complexity of combining research in the two fields.

The efficacies of the two modalities are constantly questioned by opposing parties. On the one hand, advocates of pharmacotherapy will admit to the rehabilitative properties of psychotherapy, yet deny that it has curative value, because it does not operate on the mechanisms at the core of the disease process, but address secondary issues like interpersonal relationships and self-esteem. Advocates of psychotherapy on the other hand, will point out that psychotropic drugs will alleviate major symptoms without substantially changing the underlying clinical state. Extensive drug use is also criticised because of toxic drug effects that are often irreversible; comparable outcomes in patients on drug therapy and those on placebo; the lack of studies correlating the need for prolonged therapy with the degree of the pathology; as well as lack of data relating to the natural course of the disease without treatment.

Drugs may impact negatively on psychotherapy by reducing the patients insight; the easily attained reduction in symptoms like anxiety becoming a motive to discontinue psychotherapy; and the patient adopting a passive attitude towards therapy in general. The drugs may mask feelings that are necessary for the resolution of conflicts. Positive effects of drug therapy on psychotherapy include the facilitation of therapy by reducing discomfort, improving communication. The influence of psychotherapy on drug therapy is of less concern (Karasu, 1982:1106).

2.5 CONCLUSION

The determinants of challenging behaviour are highly complex. Challenging behaviour may exacerbate a co-existing psychiatric disorder, whereas psychiatric disorders may express themselves partly in terms of a challenging behaviour (Moss *et al.* 2000:456).

Despite the reported success rate of behavioural treatment methods to reduce self-injurious behaviour and the lack of the risks that are associated with pharmacological approaches, behavioural treatment is difficult to implement on a large scale because of its labour intensive nature. It also requires the use of skilled professionals. The time lapse before positive results are seen is also problematic and unpractical in acute situations.

Pharmacological agents may provide rapid control of behaviour in some cases, yet at the price of side effects that may persist even after withdrawal. Despite lack of research–backed evidence claimed by its opponents, pharmacological intervention stays the most commonly used modality for control of problem behaviour. To the credit of psychopharmacological intervention, it must also be taken into account that the introduction of these antipsychotics and other behaviour-altering drugs contributed to the improvement of the lives of mentally retarded persons; those with behaviour problems themselves, those who have to live with them; and those who have to care for them.

Appropriate selection of drugs may lead to a better risk:benefit ratio. Opponents agree that research studies do show a decrease in target behaviour, but point out that methodological shortfalls exist in the design of these studies and that there is no mentioning of the effect of medication on adaptive behaviour and a lack of follow-up data to indicate longevity of treatment effects (Matson *et al.*, 2000:285).

The role of various neurotransmitters in the aetiology of aggression and self-injury will be explored in Chapter 3.

CHAPTER 3
BIOCHEMICAL MODELS OF AGGRESSION AND SELF-INJURY

3.1 INTRODUCTION

Aggression and self-injuring behaviour may have various aetiologies, including different psychopathological processes recognisable as defined disease states. Often, however, all the criteria to make a specific diagnosis are not present in a particular case. Researchers thus embarked on a symptom-based approach in studying the neurobiology of psychopathology. Individual symptoms rather than defined syndromes have been investigated for possible markers. It is possible that a symptom like self-injurious behaviour occurring in different conditions may share a common organic component independent of the syndrome diagnosis. The clinical implication of this line of thought is that individual symptoms may be treated individually in cases where the underlying condition may be refractory to treatment.

Evidence of the involvement of different neurotransmitters in the pathogenesis of aggressive and self-injurious behaviour has led to the development of several hypotheses regarding the underlying neuro-chemical events. The evidence for the involvement of the different neurotransmitters stems from research based mainly on observations in animal studies that was eventually applied in biological studies in humans. Evidence based on the response to different pharmacological agents also provides indirect evidence for the involvement of particular neurotransmitters.

3.2 THE SEROTONIN HYPOTHESIS

Of the more than 50 known or suspected molecules that play a role in neurotransmission, serotonin and its role in human aggression received a good deal of attention from researchers.

Two main streams of thought have fed the support for the involvement of the serotonergic system. On the one hand, there is animal data relating aggression to serotonergic depletion. On the other hand, there is the evidence provided by studies in humans. The evidence in humans rests on similarities in features of self-injurious behaviour and obsessive compulsive disorder, that also been linked to serotonergic function, as well as studies on CSF HIAA concentrations. Self-injurious behaviour in patients with co-existing OCD has been shown to respond to treatment with SSRIs (Winschel & Stanley, 1991:311).

Several hypotheses regarding the relationship between serotonin and aggression were reviewed by Berman, Tracey and Coccaro (1997).

3.2.1 The low serotonin syndrome (LSS) Model

Linnoila and Virkkunen (1992:49) proposed a model to describe the phenomenon of lack of impulse control in a sub-group of violent offenders. According to this model, decreased serotonergic function in the raphe nuclei causes a reduction in the serotonergic activity in the forebrain, eventually resulting in disturbances of diurnal rhythm regulation and glucose metabolism. Hypoglycaemia lowers the threshold for impulsive aggressive behaviour, while the alteration in the diurnal rhythm may lead to a chronic low-grade dysphoria. Mood regulation by alcohol consumption leads to eventual depression of serotonergic action. Psychological and environmental factors – apart from alcohol consumption – involved in the expression of aggression are , however, not covered by this model (Berman *et al.*, 1997:658).

3.2.2 The information–processing model

According to this model, the role of serotonin is to modulate an organism's responses to external and internal signals like hormonal and neurotransmitter systems. Serotonin stabilises information flow in neuronal circuits, leading to controlled behavioural, cognitive and affective output in the presence of changing environmental demands (Spoont, 1992:339). Again, dysregulation of serotonergic activity is not seen as specific to aggression. Reduced 5-HT levels result in "overshoot" in neuronal systems, which in turns manifests in three ways, namely exaggerated response to provocative or threatening cues; decreased sensitivity to cues associated with behavioural suppression, including nociception; and delayed recovery from behaviour (Spoont, 1992:340). The effect of low 5-HT activity on the limbic system results in a tendency to overreact as well as deficient affective stability. In conclusion then, low 5-HT renders an individual vulnerable to behavioural instability (Spoont, 1992:344).

3.2.3 The irritable aggression model

According to this model, decreased serotonin activity leads to general hyperirritability. Aggressive behaviour will, however, only occur when the organism is faced with a noxious environmental event and the neuronal systems for arousal and goal-directed behaviour (e.g. dopamine and noradrenaline) are sufficiently activated (Coccaro, 1989:52). The low serotonin leads to a lowered threshold for response to provocation. This implies that the low 5HT levels may not affect the level of aggression in the absence of provocation.

It is still unclear whether a causal relationship exists between serotonin functioning and aggression, or whether there is merely a correlation with human aggression. Berman *et al.* (1997:661) express the view that 5HT status is probably only playing a small part in complex social behaviours such as the

expression of aggression. It is likely that the link between serotonin neurotransmission and aggression may be dependent on the functioning of other neurotransmitter and hormonal systems.

If the primary neurochemical abnormality is reduced serotonin levels, it means that serotonergic drugs like the selective serotonin re-uptake inhibitors (SSRIs) may be useful in reducing aggressive behaviour. Successful treatment with various serotonergic drugs has indeed been reported. It is, however, cautioned that results may vary because the observation of decreased serotonin may be part of a dynamic disease process with initial serotonin deficiency, followed by eventual up-regulation of receptors and hypersensitivity of the system. The successful application of drugs for this indication should also not be viewed as the only or even the preferred method of intervention (Berman *et al.*, 1997:662).

3.3 THE DOPAMINE HYPOTHESIS

Breese, Chriswell, Duncan and Mueller (1990:482) demonstrated that destruction of dopaminergic neurons in neonatal rats led to hypersensitivity of the dopaminergic receptors and eventually to self-injuring behaviour. They found several similarities between the behaviour of these rats and the behaviour seen in Lesch-Nyhan syndrome and subsequently proposed a similar mechanism for the development of Lesch-Nyhan syndrome. Goldstein, Anderson, Reuben and Dancis (1985:339) proposed that the self-injurious behaviour in Lesch-Nyhan syndrome may be due to supersensitive dopaminergic receptors after initial dopamine deficiency. They distinguished between the action on dopamine 1 (D1) and dopamine 2 (D2) receptors by using fluphenazine that acts on both receptors and relieved the self-injury and sulpiride, a selective D2 blocker which did not relieve the symptoms. It was concluded that dopamine 1 receptors was involved in auto-aggression. Clozapine, with its preferential blocking of D1 should thus be a good choice from a mechanistic point of view.

Neuroleptic drugs with their dopamine blocking properties are commonly used to treat self-injuring and aggressive behaviour, although they are controversial in this setting due to the poor side effect profile, especially movement disorders and tardive dyskinesia. Craft and Schiff (1980:254) reported success with fluphenazine for the treatment of both aggressive and negativistic problem behaviour. The newer antipsychotics which are less likely to cause EPS, and unlikely to cause tardive dyskinesia should be a better option, also by virtue of its dual action on both serotonin and dopamine receptors. Clozapine and risperidone has been reported as successful (Pies & Popli, 1995:582), (Antonacci & De Groot, 2000:24).

3.4 THE ENDORPHIN HYPOTHESIS

The increased release of endorphins in response to pain stimulation may act as a positive reinforcement for self-injuring behaviour (Winschel & Stanley 1991:309). It is also postulated that alteration of the opioid system in some individuals may result in an increased demand for endogenous opiates to maintain an adequate "opiatergic tone".

Herman, Hammock, Arthur-Smith, Egan, Chatoor, Werner and Zelnik (1987:552) demonstrated the successful use of naltrexone, a long-acting opioid antagonist, in the treatment of self-injuring behaviour (SIB) in a small group of patients. They saw the result as indicative of the involvement of brain opioid peptides in SIB, more specifically the μ opioid receptors. This leads to decreased pain response and less incentive to stop behaviour. Pies and Popli (1995:582) concluded that this might be the end result of a two-phase process, following on the initial deficiency of opioid activity with eventual overproduction of opioids or hypersensitivity of the receptors. The measurement of endogenous opioids in individuals with SIB also provided evidence for a possible role for opioids.

Studies with opioid antagonists in humans have only been done on a small scale and results are inconclusive (Winschel & Stanley, 1991:310; Pies & Popli, 1995:584). Herman et al. (1989:87) caution about the use of naltrexone in children and patients with concomitant medical problems or a history of prenatal or postnatal brain trauma. These exclusions limit the possible application of the drug.

3.5 THE NORADRENALINE HYPOTHESIS

A large concentration of noradrenergic neurons occur in the locus ceruleus, located in the midbrain, below the fourth ventricle from where they project to virtually all areas of the brain. Projections to the cortex affect high-degree learning, while projections to the amygdala affect emotions and through projections to the thalamus and hypothalamus, they also affect the pituitary-adrenal axis. The low and fairly regular firing of the neurons' discharge is mainly controlled by the alpha 2 adrenoreceptors. In the event of overactivation due to excessive noradrenaline, the firing activity is inhibited through the alpha 2 adrenoreceptors. The release of endogenous noradrenaline is highly dependent on electrical impulse flow; if the firing rate of noradrenergic neurons is high, more noradrenaline is released through the brain (Blier, 2001:2 of 6).

Haller *et al.* (1998) described the role of the catecholamines in the control of aggression. Involvement of the catecholamines takes place on three levels, namely:

1. The central nervous system where it plays a part in information processing, assessing the relevance of environmental stimuli. It subsequently controls endocrine, metabolic, physical and behavioural responses to a perceived threat.
2. The sympathetic system through which a wide range of effector organs are affected, including muscles and the adrenal medulla, preparing the organism for possible confrontation.

3. The adrenal medulla where adrenaline and noradrenaline act as hormones to control the metabolic processes needed to fuel the physical demands of the aggression response.

These three systems react rapidly to environmental challenges and activate the organism as a whole.

Noradrenaline indirectly affects the aggression response in that it enhances arousal and vigilance; decreases pain perception beyond opioidergic control; and enhances olfaction and memory to facilitate recognition and learning. These indirect preparatory actions may be the only involvement of noradrenaline in aggression, yet it cannot be excluded that it might exert a direct effect on aggression as well. Noradrenaline might have a certain degree of specificity, enhancing the behavioural effects of other hormones.

The noradrenergic and serotonergic systems interact with each other and a drug like mirtazapine that increases noradrenaline firing, also causes a temporary increase in serotonergic activity (Blier, 2001:3 of 6).

3.6 CONCLUSION

Complex behaviour patterns may be the result of interactions between different neurotransmitters, rather than to the activity of one neurotransmitter system alone. There are many overlaps between the effects of noradrenaline, serotonin and dopamine. Vigilance seems to be controlled by noradrenaline, but noradrenaline also influences anxiety and irritability, a function shared by serotonin. Serotonin controls impulsive behaviour, yet shares an influence on appetite, sex and aggression with dopamine. Dopamine is responsible for euphoria and pleasure, but also affects motivation and energy, like noradrenaline.

In addition to its theoretical significance, the functional overlap of the different neurotransmitter systems has important implications for the conduct of psychiatric research. A possible link between elements of impulse decontrol

and serotonergic dysfunction may be the common element in aggression and self-injury (Winschel & Stanley, 1991:311). The implications for treatment are that if a clear deficiency is identified in one system, manipulating a communicating neurotransmitter system may attain the desired response. Blier (2001:4 of 6) expresses the view that if reliable probes for the determination of neuronal function in humans can be developed, it may be possible to identify the appropriate drugs for a given patient without relying on a trial-and-error approach.

The role and function of the hypothalamic-pituitary-adrenal axis and the hypothalamic pituitary-thyroid axis, their relation to neurotransmitter action, as well as the functional assessment thereof will be discussed in Chapter 4.

CHAPTER 4

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS FUNCTION AND HYPOTHALAMIC-PITUITARY-THYROID AXIS FUNCTION

4.1 INTRODUCTION

The hypothalamus integrates information received from both the internal and the external environment of the body and orchestrates the response of the body to changes in the environment. Exposure to hostile conditions leads to the so-called " stress responses", aimed at improving the probability of survival in adverse situations. The stress response involves adaptations to multiple organ systems, including altered behaviour, autonomic and hormonal function (Carrasco & Van de Kar, 2003:236).

The physiological changes involved in the stress response include the mobilisation of energy; enhanced alertness and focus; adaptations to cerebral blood flow and glucose metabolism; cardiovascular and respiratory adaptations; modulation of the immune response as well as adaptations in sexual and feeding behaviour (Carrasco & Van de Kar, 2003:236). Adaptive behavioural changes are an integral and major component of the stress response. Overstimulation of the normal activation systems leads to the pathological expression found in anxiety disorders and depression. With chronic overactivation damage to other target organs follows. The neurobiological mechanisms involved in the process include activation of the HPA axis and the autonomic nervous system (Koob, 1999:1167).

4.2 THE HYPOTHALAMIC-PITUITARY AXIS

The hypothalamus-pituitary complex receives information from diverse sources. The hypothalamus exerts its regulatory function through the secretion of so-called hypothalamic hypophysiotropic hormones (HHH). Among these are the thyroid-releasing hormone (TRH), corticotropin-releasing factor (CRF) and prolactin inhibiting factor (PIF). These substances are transported via the portal vessel to the anterior pituitary, where they trigger the release of the pituitary hormones (Nemeroff & Prange, 1978:1004). TRH, for instance, will lead to the secretion of thyroid-stimulating hormone (TSH) and CRF to the secretion of adrenocorticotrophic hormone (ACTH). Some of the HHH are, however, not entirely specific in their action. For instance, TSH also causes the release of prolactin (Nemeroff & Prange, 1978:1005).

CRF functions as both a neurotransmitter and a mediator between the central nervous system and the endocrine system. As such, it mediates the effect of stressors on the hypothalamic-pituitary-adrenal (HPA) axis and controls the endocrine, autonomic, behavioural and immune responses to stress (Carrasco & Van de Kar, 2003:237). The neuro-endocrine function of CRF manifests in its central role in the control of ACTH release from the anterior pituitary.

CRF neurons also project to the locus coeruleus, which controls the noradrenergic system. "Evidence suggests that CRF acts as a neurotransmitter in the locus coeruleus – mediating noradrenergic activation by various stressors" (Carrasco & Van de Kar 2003:247). Koob (1999:1176) proposes that stress activates two forms of CRF-noradrenaline interactions, potentiating each other through a feed-forward system. This results in progressive augmentation with repeated exposure to stressors. Both CRF and noradrenergic neurons are stimulated by serotonin and acetylcholine and inhibited by glucocorticoids, gamma amino butyric acid (GABA), ACTH and opioid peptides (Carrasco & Van de Kar, 2003:237). Serotonergic neurons interact with CRF neurons. The regulation of serotonergic firing by CRF may be an important mechanism for mediating serotonergic dysfunction in

neuropsychiatric disorders such as anxiety and depression (Carrasco & Van de Kar 2003:246). CRF directly modulates learning and memory processes with secondary effects on the acquisition and maintenance of behaviour processes (Nemeroff & Prange, 1978:1000).

Two CRF receptor subtypes, CRF1 and CRF2, can be distinguished in mammalians. Antagonists of CRF1 show promising results regarding antidepressant and anxiolytic activity. The CRF2 receptor seems to be linked to eating behaviour and may become the target in eating disorders. Nemeroff (2002:15) foresees that a CRF1 receptor antagonist for the treatment of depression and anxiety will soon become a reality.

4.3 THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

ACTH is released by the anterior pituitary and regulates the release of glucocorticosteroids by the adrenal gland. The glucocorticosteroids not only play an important part in energy metabolism, immune response and brain function – including memory and learning which underlie behavioural responses – but also regulate the HPA axis through termination of the stress response via its negative feedback action on the hypothalamus and pituitary.

The hippocampus is also specifically implicated in depression. This structure in the limbic area of the brain appears to be particularly vulnerable to the effects of stress. Early adverse life-experience may cause long-lasting changes in the hippocampal physiology, leaving the individual prone to mood disorder in later life. Duman, Nakagama & Malberg (2001: 837) and Reid and Stewart (2001: 301) discuss the relationship between stress, depression and hippocampal function. Exposure to stress causes hyperactivation of the HPA axis; elevated corticosterone levels act as a neurotoxic agent to the vulnerable neurons of the hippocampus; this leads to impaired neurogenesis in the hippocampus, In addition, stress down-regulates the expression of a protective neurotropic protein" brain-derived neurotropic factor" and eventually

impaired control of mood as well as impaired inhibitory control of the HPA axis occur. An increased level of the HPA axis hormones, including cortisol, is seen as a measure of stress (Courtney De Vries, 2002:405).

The relationship between HPA function and mood disorders is well demonstrated by the high prevalence of symptoms of mood disorders in patients with adrenocortical dysfunction such as Cushing's and Addison's or with exogenous administered glucocorticosteroids. Correction of the HPA function in these patients leads to euthymia. Hypersensitivity of the HPA axis, on the other hand, is strongly associated with major depression, with a correlation of 50-95 % non-suppression in subjects with major depression and 5-10 % in normal controls (Nemeroff, 1989:16). Besides the demonstration of non-suppression during DST, elevated CRF measurements in CSF have been demonstrated in patients with major depression and suicide victims (Nemeroff, 1989:17). These findings led to the hypothesis that CRF may be hypersecreted in depressed patients. The elevation of cortisol in depression is state dependent, as it normalises after treatment.

4.4 THE HYPOTHALAMIC-PITUITARY-THYROID AXIS

TRH containing neurons receive afferents from a variety of CNS neurons and in response to stimulation they release a tripeptide, TRH, in the medial eminence of the hypothalamus, from where it is transported to the anterior pituitary. Here it binds to a specific membrane receptor on the thyrotrophs, resulting in increased synthesis of TSH. TRH also leads to the release of prolactin as well as somatostatin. TSH is released into the general circulation and eventually binds to membrane receptors in the thyroid gland, resulting in an increase in the synthesis and release of the thyroid hormones, T3 and T4. These hormones provide feedback to hypothalamic and pituitary level to control the level of TRH and TSH. Somatotrophin release inhibiting factor (SRIF) and cortisol also exert a negative feedback.

The overlap in symptomatology between mood disorders and thyroid dysfunction is well known. Symptoms of mood disorders occur in patients with thyroid disease and likewise, primary hypothyroidism should be ruled out before a diagnosis of major depression can be made (Nemeroff, 1989:13). Patients with hyperthyroidism may also exhibit mental changes that may occasionally be confused with anxiety or panic disorder. TRH has been reported to produce beneficial effects in conditions like depression, mania, alcohol withdrawal, schizophrenia, hyperkinetic syndrome in children, as well as childhood autism. In normal subjects it induces mild euphoria and relaxation.

A blunted TSH response to TRH stimulation is seen in 25 % of patients with major depression and normal baseline TSH and thyroid hormones. The underlying mechanism for this phenomenon is unknown. It may be secondary to chronic hypersecretion of TRH with resultant down regulation of TRH receptors. It is still unresolved whether the blunted response is a state or trait marker (Nemeroff, 1989:15).

In 15 % of patients with major depression, an exaggerated response to TRH is found. This finding is associated with a significant percentage symptomless auto-immune thyroiditis (SAT) (Nemeroff, 1989:14), especially in patients with bipolar mood disorder.

Thyroid hormones on their own do not have an antidepressant function, yet may accelerate the onset of antidepressant effect (Prange, Wilson, Lipton, Rabon, McClae & Knox, 1970:443).

Dopamine can also influence the secretory activity of the TRH cells by inhibition of prolactin secretion. Excess dopamine activity may also account for blunted TSH response, as demonstrated by the administration of L-dopa and dopamine.

4.5 ASSESSMENT OF HYPOTHALAMIC-PITUITARY-ADRENAL AXIS FUNCTION AND THE DEXAMETHASONE SUPPRESSION TEST

Cortisol levels are regarded as indicative of stress. During major depression, however, there is more subtle HPA axis dysfunction. Carroll (1982:292) describes the development of the DST, initially introduced by Liddle in 1960 for the study of Cushing's disease, into a tool to assess these subtle changes. A popular method of screening for Cushing's disease, a single dose of dexamethasone in the late evening followed by cortisol measurements early the next morning, was used to determine HPA function in depressed patients. This method yielded abnormal results in about 40 % of melancholic patients. Carroll later demonstrated that the depressed patients might often not show non-suppression during the early morning, but that they escape from suppression later in the day. However, normal patients will remain suppressed for at least 24 hours. The test was subsequently adapted to include two additional blood samples, at 16:00 and 23:00. An elevation in the cortisol level at either of these times would indicate abnormal inhibition of HPA function.

4.5.1 Method

Carroll (1982:294) recommends the following method: 1mg of dexamethasone is administered orally at 23:00. Blood samples for cortisol assessment are taken at 16:00 and 23:00 the next day, with minor variations of ± 1 hour from these times having little influence on the outcome of the test. A plasma cortisol level of more than 5 μg/dl (138 nmol/L) in any of the samples is abnormal.

4.5.2 The significance of non-suppression

It is unclear whether changes in monoaminergic systems cause hyperactivity of HPA axis or whether changes in the monoaminergic systems are secondary to CRF hypersecretion (Nemeroff, 1989:18).

Evidence strongly suggests that Corticotropin-releasing hormone hypersecretion contributes to HPA axis hyperactivity in depressed patients (Nemeroff 1989:17; Calfa, Kademian, Ceschin, Vega, Rabinovich & Volosin, 2003:688). Additionally, an impaired feedback inhibition by endogenous corticosteroids might contribute to the hypersecretion of CRF and the resultant hypercortisolaemia. Sapolsky, Krey and Mc Ewen (1986:285) describe this process as a consequence both of stress and the ageing process.

One mechanism responsible for the CRF hypersecretion may be an altered feedback inhibition of CRF release by glucocorticoids. Endogenous glucocorticoids serve as potent negative regulators of the expression and release of CRF through binding to glucocorticoid receptors in brain areas that regulate HPA axis activity (Calfa *et al.*, 2003). A diminished number of glucocorticoid receptors (GR) underlie the HPA axis hyperactivity. The number of GR increases after treatment with antidepressants.

The DST is a measure of the functional integrity of the GR-mediated negative feedback mechanism at the pituitary level (Calfa *et al.*, 2003). The magnitude of dexamethasone non-suppression may be directly related to the severity of the depression (Evans, Burnett & Nemeroff, 1983:588). Dexamethasone non-suppression returns to normal after remission, thus constituting a state–dependent marker (Nemeroff, 1989:17). Although stress is known to activate the HPA axis (reflected by elevated cortisol levels), it does not appear as if stress on its own results in escape from dexamethasone suppression.

4.6 ASSESSMENT OF HYPOTHALAMIC-PITUITARY-THYROID AXIS FUNCTION AND THE THYROID RELEASING HORMONE STIMULATION TEST

The measurement of TSH concentration in the serum after administration of TRH is inexpensive, safe, rapidly accomplished and does not require a high level of patient co-operation (Loosen & Prange, 1982: 405). The administration of synthetic TRH challenges the anterior pituitary to respond and differences in the TSH responses are characteristic of one or another disorder in the HPT axis. The results should also take into consideration the baseline TSH levels to distinguish between primary hypothyroidism (low baseline thyroid hormones plus high resting TSH and TSH response) and pituitary hypothyroidism (low baseline thyroid hormones and low/normal Baseline TSH and TSH response). A diminished TSH response to TRH found in mental patients cannot be explained from an endocrine perspective. In most studies thyroid hormone levels as well as baseline TSH levels were normal. The pathophysiological significance of these findings may be increased TRH activity (Loosen & Prange, 1982: 413), (Nemeroff 1989: 15) or alternatively, increased dopamine activity may lead to a blockade of the TSH response to TRH (Loosen & Prange, 1982: 413). A blunted response has been demonstrated in depression; some patients with mania, anorexia nervosa and alcoholism.

An exaggerated response has also been demonstrated in about 15 % of depressed patients. In these patients a correlation of 20 % with symptomless auto-immune thyroiditis (SAT) has been demonstrated (two to four times normal) (Nemeroff, 1989:14). The presence of SAT was also higher in patients with an abnormal DST.

Factors other than thyroid conditions that may influence the test include increasing age, male sex, acute starvation, chronic renal failure, Klinefelter syndrome and repetitive administration of TRH and administration of somatostatin and neurotensin, dopamine, thyroid hormones or glucocorticoids. Loosen, Kistler and Prange (1983:703) found that factors

such as thyroid hormones, cortisol, weight, height and body surface do not influence the test.

4.6.1 Method

After overnight fasting, a fixed amount of TRH (200-500 microgram) is administered intravenously, usually in the morning. The patients are kept resting and the blood pressure is monitored every five minutes after administration for the first 15 minutes. Blood levels of TSH are measured every 30 minutes for two to three hours (Nemeroff, 1989:14). Kirkegaard, Norlem, Lautidsen, Bjorum and Christiansen (1975:1115) timed the sampling of TSH at 20 minutes and 60 minutes after the intravenous administration of Proterilin.

4.6.2 The significance of a blunted response

The anterior pituitary is regulated not only by feedback messages from the pituitary, but also by hormones secreted by the hypothalamus. The hypothalamic neurons, in turn, are regulated by nerve cells in other parts of the brain, exerting their effect on the hypothalamus through the secretion of various neurotransmitters. Loosen and Prange (1982:411) suggest that patients who show a blunted TSH response may have a hypersecretion of TRH. Initially hypersecretion of TRH will cause hypersecretion of TSH and that, in turn, may lead to a transient thyroid activation. After chronic hypersecretion of TRH, the pituitary becomes hyporesponsive to TRH, posssibly due to down-regulation of the pituitary receptors.

Noradrenaline and dopamine appear to stimulate TRH cells, while serotonin appears to mainly to inhibit them. The influence of dopamine, however, seems to be inactivated when the conversion of dopamine to noradrenaline is blocked. Increased TRH activity can thus be explained by either reduced input of serotonergic input or increased noradrenaline input.

4.7 CONCLUSION

The HPA axis and the HPT axis either represent the sum total of the input of various neurotransmitters or may influence the mono-aminergic systems. The HPA axis is associated with serotonergic function, while the HPT axis is associated with dopaminergic, noradrenergic and serotonergic systems. The necessity of distinguishing between the actions and relative contributions of different mono-aminergic systems in a complex pathological behaviour pattern such as aggression may be eliminated if a relationship exists between the particular behaviour and dysfunction of a particular neuro-endocrine axis. The dysfunctional neuro-endocrine axis may thus become the target for intervention, rather than individual mono-aminergic systems. Furthermore, the axis dysfunction may be used as a monitoring tool, independent of the fluctuating nature of the clinical presentation.

The ethical considerations regarding research in mentally retarded persons as set out by international and statutory bodies, as well as unresolved challenges in this area, will be described in Chapter 5.

CHAPTER 5
ETHICAL CONSIDERATIONS REGARDING RESEARCH IN MENTALLY RETARDED PERSONS

5.1 INTRODUCTION

Researchers in the field of mental retardation constantly face the challenge of balancing the demands of proper research methods with the requirements for ethical practices. A constant tension exists between the need to develop new treatment methods and the importance of protecting the rights of a vulnerable research population. Haywood (1976:312) argues that the mentally retarded should have the right to the best care, treatment, education and habilitation, yet are currently not privileged to that right due to the widespread lack of knowledge in this field. As such, neglecting this area of research may also be unethical.

It is accepted that biomedical experimentation on humans is an essential final component of the process of drug development and that abolishing human experimentation will impact negatively on scientific and medical progress, as intra-species variation does not allow for the direct extrapolation of animal data to humans. It can also be argued that a "collective social and ethical duty" rests on individuals to participate in experiments towards the benefit of mankind. However, this does not mean that participation must be involuntary (Baudouin, 1990:1052).

The atrocities of medical experimentation on mentally retarded persons and other disabled persons committed by the Nazis prior to the Second World War, as well as other unethical research reported elsewhere, have underlined the need for setting guidelines for the limits of ethical and legal experimentation in humans. These guidelines have to allow for safe, voluntary research of true scientific value. The process involved in setting these guidelines requires that the scientific value of the research should be

established, informed voluntary consent must be obtained and an acceptable risk:benefit ratio for the subject must be maintained (Baudouin, 1990:1053).

Researchers who participated in the Nazi experiments were brought to justice during the Nuremberg Doctors' Trials after World War Two. The Nuremberg Code of 1947, which was developed as a result of these proceedings, established that informed, voluntary consent of a human subject was absolutely essential. It further established the right of an individual to refuse to participate in research and to terminate research participation at any time. It prohibited all kinds of research on the mentally handicapped, ruling that a prospective research subject should have the capacity to give consent. The Declaration of Helsinki of 1964, revised in 1975, allows experimentation on the provision that substituted consent is legally obtained (Baudouin, 1990:1056). The Declaration of Hawaii of 1977 states that only experimentation necessary for the development of psychiatric knowledge is allowed on persons who are mentally incompetent (Baudouin, 1990:1056).

5.2 THE HELSINKI DECLARATION

The Helsinki Declaration is a statement of the World Medical Association with the purpose of guiding the medical profession in medical research involving human subjects. The declaration was adopted in June 1964 and subsequently amended in 1975, 1983, 1989, 1996 and 2000.

The declaration acknowledges the fact that medical progress is dependent on research and that research ultimately partly involves human experimentation. The well-being of the human subject is, however, regarded as more important than the interests of society. Special attention is devoted to specific research populations who are regarded as vulnerable, including the mentally retarded.

The general duties of the physician involved in research include the protection of human life, health, privacy and dignity and complying with generally

accepted scientific principles, based on thorough knowledge of the scientific literature.

Intended research has to be formulated in a formal experimental protocol that needs to be approved by a specially appointed ethical review committee that should act within the laws and regulations of the particular country. Possible sources of conflict of interest, as well as issues regarding monitoring of the project, need to be declared to the committee. Risks and benefits need to be assessed and "medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research" (RSA DoH, 2000:57).

The declaration states that research that involves groups who are mentally incompetent should involve obtaining informed consent from a legally authorised representative in accordance with applicable law. A subject that is legally incompetent may be able to assent to a procedure and a researcher should obtain assent in individuals who are capable of giving assent additional to the consent given by the authorised representative (RSA DoH, 2000:58).

5.3 THE ROLE OF STATUTORY BODIES IN SOUTH AFRICA

The document *Guidelines for good practice in the conduct of clinical trials in human participants in South Africa* outlines the roles and responsibilities of the various parties involved in clinical trials in South Africa. The guidelines were set in compliance with the legislative and regulative framework relevant to the South African context. The purpose of the guidelines is to "ensure that clinical trials conducted on human participants are designed and conducted according to sound scientific and ethical standards" (RSA DoH, 2000:1).

5.3.1 The Medicines Control Council

As the regulatory authority, it is the responsibility of this council to ensure that the drugs available in the country are safe, of good quality and effective. All clinical trials of non-registered medicinal substances and new indications of registered medicines must be reviewed by this body. The council may close a trial down should there be serious contravention of the code of Good Clinical Practice.

5.3.2 The National Health Research Ethics Council

This body reports directly to the Minister of Health and is responsible to "promote, ensure and monitor compliance" of the local ethical committees with legislation, regulations and ethical guidelines (RSA DoH, 2000:5).

5.3.3 Ethics Committees

The ethics committees are responsible for protecting the rights, safety and well-being of participants in trials through reviewing, approving and commenting on the suitability of investigators, facilities, methods and procedures used to obtain informed consent.

Ethics committees must take special cognisance of specific vulnerable groups, including people with mental disabilities, prisoners and children. People with mental disabilities include those with cognitive or developmental disabilities as well as those with psychiatric disorders. Institutionalisation is seen as an additional factor in compromising decision-making ability.

5.3.4 Guidelines applicable to research in mentally retarded persons

According to *Guidelines for Good Clinical Practice in The Conduct Of Clinical Trials In Human Participants In South Africa Clinical Trials Guidelines* research in people with cognitive disabilities must:

- "Be relevant to the mental disabilities ..so that it is necessary to involve people who are mentally disabled ...
- Provide sufficient justification for involving people with mental disabilities ...who are institutionalised as the study population
- Ensure appropriate evaluation procedure for ascertaining participant's ability to give informed consent. If participants are deemed unable to understand and to make a choice, then an appropriate individual, able to consent on their behalf must be sought.
- Ensure that consent is free form coercion and risk to patients
- Ensure that no more than minimal risk is involved, or if minimal risk is involved, the risk is outweighed by the anticipated benefits of the study for the participants and the importance of the knowledge which will emanate from the research" (RSA DoH 2000: 12).

5.4 ETHICAL CHALLENGES IN RESEARCH IN MENTAL RETARDATION

Although some issues are clearly spelled out, there remains a number of grey areas that the researcher has to face.

5.4.1 Consent capacity

A central problem in dealing with consent in the mentally retarded is the difficulty or impossibility of obtaining true informed, voluntary consent. Allowing an optimal degree of autonomy of potential subjects and the protection of vulnerable persons are important issues given the limitations in

the decision-making process for this population due to cognitive impairment or lack of information and support.

Stineman and Musick (2001:11) distinguish between the terms "competency" and "decision-making capacity". While "competency" denotes a legally constituted entity, "capacity" refers to the specific ability of a person to understand the risks and benefits involved to him personally if involved in a study or to use this information to make a decision and to communicate that decision. Ensuring informed consent will mean that information supplied to the subject should be presented in an understandable manner for the particular subject. The subject must also understand the voluntary nature of consent. Manipulation and coercion constitute extreme forms of threat to voluntariness, but on a more subtle level undue influence, unrealistic therapeutic optimism or excessive paternalism may also compromise voluntariness (Stineman and Musick, 2001: 12).

5.4.2 Assessing consent capacity

There are no established standards, measures or mental status tests to assess consent capacity. Baudouin (1990:1054) expresses the opinion that with a mentally retarded person who is declared incompetent by law, yet has the capacity to understand and react to information, there is no reason from an ethical point of view to treat this person differently from any other person.

An investigator can assume an individual is capable to make a decision if he/she is able to communicate choices; to understand relevant information; to appreciate a situation and its consequences; and to manipulate information rationally (Appelbaum & Grisso, 1988:1636). Dubler (1987:547) reasons that a patient may still be able to provide a legally effective consent in the presence of mental deficits. The degree of decisional capacity required must be adapted to the specific risk:benefit ratio for the subject in the proposed study. A patient may therefore have the capacity to give consent for an observational study, but not for a phase one drug trial.

5.4.3 Voluntariness

Voluntariness implies that the subjects should be able to make decisions "freely and without coercion" and that they may end their participation without fear of retribution. Arboleda–Flòrez and Weisstub (1997:485) draw attention to the vulnerability of institutional residents, caused by their dependency on others and general lack of freedom. The involvement of institutionalised individuals in research should be sufficiently justified (Freedman, 2001:134). To minimise the risk of exploitation, there should be a limit to "the level of risk to which institutionalised mentally disordered persons may be subjected" (Arboleda–Flòrez & Weisstub, 1997:489).

5.4.4 Surrogate decision-making

The real problem regarding consent arises when the potential subject is affected so severely that there is no possibility of obtaining informed consent. A surrogate or proxy is often asked to provide informed consent in the place of an individual who is judged to be incapable of providing informed consent. Family members or guardians are often involved (Freedman, 2001:135).

Traditionally, there are two standards in making proxy decisions on behalf of individuals that are mentally incapable of exercising rational decision-making, namely "substituted judgement" and "best interests." Substituted judgement" means that a decision is made based upon the surrogate's knowledge of what the individual would have decided if she or he was competent. It relies on the surrogate's judgement of the incapacitated individual's personal values, preferences, and past experiences. This requires the incapacitated individual to have been competent in the past. Many mentally retarded persons have, however, never been competent (Freedman, 2001:135).

If substituted judgement is not possible, the "best interest standard" is used. The surrogate bases the decision regarding participation upon the individual's best interests. The surrogate should thus assess the risk–benefit ratio of the

proposed research. Ideally, minimal risk with maximal potential for therapeutic benefit should exist (Freedman, 2001:135).

Freedman (2001:139) advises that surrogate decision-makers should be instructed with regard to the exercise of appropriate substituted judgement and best interests standards. Surrogate decision-makers should acquire the ability to distinguish between their own feelings and that of their charge(s).

5.4.5 Assessing risk and benefit

Acceptable risk and potential for therapeutic benefit are not quantifiable. The surrogate has to base his/her decision on the best interest of the individual without the help of clear guidelines (Freedman, 2001:136). Minimal or no risk is regarded as acceptable for vulnerable groups such as the mentally handicapped (Baudouin, 1990:1053). "Minimal risk" is not defined by the *Guidelines for Good Practise in the conduct of clinical trials in human participants in South Africa*. Freedman (2001: 136) quotes the *Federal Policy for the Protection of Human Subjects* which describes minimal risk as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests". "Minimal risk" may, however, not mean the same in different individuals (Freedman, 2001:136).

Clinical studies involving methodologies such as randomisation, control groups and double blind procedures may be especially difficult for potential research subjects to comprehend to recognise that participation in clinical trials may not necessarily be personally beneficial or therapeutic (Freedman, 2001:136).

Participation in research that does not involve therapeutic benefit is particularly controversial. The Nuremberg Code prohibits non-therapeutic research involving mentally impaired subjects. Baudouin (1990:1055) argues

that the proxy consent can only be given for the benefit and in the best interest of the handicapped person. Non-therapeutic experimentation is never for the benefit of the subject or in his/her best interest and as such is impermissible. Arboleda-Flòrez and Weisstub (1997:S489) propose that a surrogate decision-maker should not be allowed to give consent to research that constitutes more than a low risk. As the level of risk increases, judicial or quasi-judicial review should be instituted.

Freedman (2001:136) advises that the required level of decision-making capacity for a particular research protocol should be balanced with the specific risks and benefits of the research involved. A high level of decisional capacity should thus be present in research involving high risks and minimal or no therapeutic benefit for an individual. A lower level of capacity may be adequate to make decisions regarding research with minimal or no risk and a strong element of therapeutic benefit.

Fulford and Howse (1993:86) argue that the academic backlog that psychiatry has in comparison to other medical disciplines, may make it difficult to assess the likely clinical usefulness or inherent risks of a research project with confidence. However, the clinical relevance of the project will generally be clear.

5.4.6 Assent of research subjects

Assent involves the willingness of the subject to participate in the study. It is important to obtain assent from the prospective research subject in addition to surrogate consent for research participation (Freedman, 2001:137).

Freedman (2001:138) proposes the implementation of continuous communication processes among researchers, research subjects, and their families. This communication process should facilitate the decision-making process. Preparatory training for prospective research subjects about decision-making and risk-taking and information about the research should be

adapted to the appropriate level of understanding. Visual aids or role-play scenarios are suggested as possible aids to improve decision-making capacity. Prospective subjects need to express their values and preferences. Researchers need to be sensitive in reading an individual's preferences, whether expressed verbally or behaviourally. Close family and friends may provide important information that can help guide the decision-making process. They can also help in providing an environment that is conducive to the individuals asking questions and expressing their concerns (Freedman, 2001:139).

Even if individuals are unable to provide informed consent, they may still be able to exercise a minimal degree of choice through expressing feelings. Good faith efforts to obtain co-operation should be the norm (Dresser, 1996:69). In respect of objecting decisional incapable subjects, Dresser (1996:69) states that investigators must have " compelling evidence that the research offers a strong prospect of significant direct benefit to the subject" to justify coercion. In the case of a persistently objecting subject, it is therefore best to exclude such a subject, be it at the beginning or during the course of the research. An alternative approach would be to limit the risk to which a decisional incapable individual may be exposed.

5.5 CONCLUSION

The expression of human psychopathology can only be appreciated to its full extent in humans. Human experimentation in psychiatric research at large is therefore a necessity for the development of scientifically based treatment methods. The conflict between the protection of the integrity and maintaining the autonomy of the individual and the need to develop treatments for mental diseases and to develop scientific knowledge is theoretically impossible to solve. Constantly excluding mental retardates from research may, however, contribute to marginalising the very real and unique problems that this population faces. Although the ethical dilemmas at ground level should not be

underestimated, an exaggeration of the ethical problems may inhibit research with the ones who may need it most, namely the most incapacitated ones.

A compromise is therefore necessary, taking into account the special vulnerability of this community and allowing optimal autonomy in the decision-making process, as well as guarding against excessive risks, while pursuing the expansion of knowledge regarding the specific problems of this population.

"Provided therefore, a humane and sensitive approach is adopted, and that the agreement of close relatives and caregivers is obtained, research at least with assenting adult incompetent patients is unlikely to be regarded as unethical' (Fulford & Howse (1993:88).

Subsequently, the methodology applied in this study will be described in Chapter 6.

CHAPTER 6
METHODOLOGY

6.1 PARTICIPANTS

All subjects were institutionalised mentally retarded patients from the Kosmos Care and Rehabilitation Centre at the Free State Psychiatric Complex in Bloemfontein. A database of all patients on antipsychotic medication was compiled during April and May 2002 and this served as the main reference for initial selection purposes. The database included particulars regarding the reason for antipsychotic drug use and a synopsis of the drug history. A preliminary selection was made from this database and consent obtained before the final selection process.

6.1.1 Selection criteria

An aggressive group and a non-aggressive group was selected according to the selection criteria described below.

6.1.1.1 *Aggressive group*

The characteristics of this group was a follows:

- Adult male and female patients, aged 20-60.
- Functioning level: IQ below 50 (according to the Fairview scale routinely done on patients at the Centre).
- On treatment with antipsychotic drugs for self-injuring or aggressive behaviour.

A total of 15 male patients and 10 female patients were selected for this group.

6.1.1.2 *Non-aggressive group*

The non-aggressive group was selected to compare the results in a non-medicated group of mentally retarded patients without the target behaviour. The selection criteria were as follows:

- Adult male and female patients, aged 20-60
- The members of the group were matched with the aggressive group for gender, age and level of functioning.
- Functioning level: IQ below 50 (Fairview scale)
- Absence of self-injuring or aggressive behaviour
- Not on antipsychotic drugs

A total of 20 male patients and 10 female patients were selected for this group.

6.1.2 Exclusion criteria

The following exclusion criteria were applied for both groups:

- Physical illness
- Epilepsy (Proterilin may cause convulsions)
- Known abnormal thyroid function (may affect results of TRHST)
- Asthma or chronic obstructive airways disease (TRHST may elicit bronchospasm)
- Known endocrine disorders (Cushing's syndrome)
- Serious weight loss*
- Obesity*
- Diabetes Mellitus (may be aggravated by dexamethasone)
- Uncontrolled high blood pressure (TRHST may cause transient fluctuation in blood pressure)
- If informed consent could not be obtained
- If the subject would not co-operate.

- Treatment with
    - Carbamazepine, phenobarbitone or phenytoin
    - Corticosteroids
    - Antithyroid drugs
    - Lithium carbonate within six months prior to test
    - Reserpine
    - Oestrogen containing preparations

[*Persons with a body mass index of below 16 and above 29 were excluded (normal range 20-25). The extended range for inclusion was due to the fact that dysmorphologic features are common in the study population, for instance microcephalus or spastic limbs with underdeveloped muscle weight. The use of antipsychotics may also lead to considerable weight gain or weight loss.]

Unforeseen cancellations had to be made when subjects proved to be unco-operative or had poor veins and access to the veins was unsuccessful. Subjects were also excluded if a suitable match could not be found.

6.1.3 Matching

Subjects were matched according to level of functioning, age and gender.

The Centre's internal evaluation of patients' functioning by means of the Fairview scale was used as the measure of functioning level for matching purposes. Initially the evaluations of 2000 were used, but during February 2003 an updated report of evaluations done during 2002 were made available. Major adaptations had to be made to update the selection and matching of patients to this new report.

Subjects were grouped in the following functioning levels:

- Moderate mental retardation: Functioning age of 36-72 months on the Fairview scale (corresponding IQ± 35-50).
- Severe mental retardation: Functioning age of 12-36 months on the Fairview scale (corresponding IQ± 20-35).
- Profound mental retardation: Functioning age of less than 12 months on the Fairview scale (corresponding IQ less than 20).

A maximum age difference of 10 years was allowed between matches.

6.2 PROCEDURES AND METHODS

The research protocol was approved by the Ethics Committee on condition that a second doctor should be available to assist should there be any adverse effects during the execution of the thyroid-releasing hormone stimulation test. Permission to work at the centre was obtained from the Chief Executive Officer of the Academic Complex, Dr S. Kabane.

6.2.1 Procedure for obtaining consent

The social workers of the Centre were presented with name lists of possible candidates for inclusion in the study in order to obtain the contact details of the nearest of kin. In cases where family contact existed, the information documents were posted with an accompanying letter to the parents or guardians in order to obtain consent. In cases where no family contact existed (no family visits and no response to letters from the institution), the management of the complex was asked to provide consent for the procedures. Both the Senior Executive Officer as well as the academic head of the Free State Psychiatric Complex were provided with a full research proposal, including the protocol.

6.2.2 Physical examination

In cases where consent had been obtained, the prospective subjects underwent a final evaluation for inclusion in the study. The purpose of this evaluation was to exclude individuals who showed any of the conditions listed under the exclusion criteria.

6.2.3 Assessing aggression and self-injurious behaviour

In the first place, a long-term profile was compiled from the subject's notes and interviews with the staff. The behaviour of aggressive subjects was graded according to frequency and intensity of aggressive episodes during the preceding 5 years. Intensity was graded as mild, moderate or severe according to the amount of damage inflicted. Frequency was graded as daily, weekly to monthly and intermittent episodes.

In the second place, the subjects were observed for a four-week observation period during which staff specifically noted the particular target behaviour on an observation chart. The observation charts were supplemented by the hospital notes of that particular period.

6.2.4 Biochemical assessment

The biochemical assessment of the collected blood samples consisted of:

- Baseline T4, TSH, prolactin and cortisol levels
- The dexamethasone suppression test as adapted by Carroll (1982:294) to assess the function of the hypothalamic-pituitary-adrenal axis.
- The thyroid-releasing hormone stimulation test to assess the function of the hypothalamic-pituitary-thyroid axis.

The investigator herself performed all the procedures on the subjects.

6.2.4.1 *Procedure for the thyroid-releasing hormone stimulation test*

Prior to the performance of the thyroid-releasing hormone stimulation test, the resident medical officer was contacted to be on standby should there be any serious side effects. (This was a condition set by the Ethics Committee.) The investigator took personal responsibility for the availability and completeness of the necessary resuscitation equipment and drugs during the procedures.

Patient compliance during procedures was critical. In cases where the subjects had adequate communication skills, the procedure was explained in terms of what it physically entailed. One of the patients stated that he was too afraid of the needles and was consequently eliminated. Two other subjects who were lower functioning were also eliminated because it became clear that they could not tolerate the cannules.

Two subjects could be comfortably assessed during one sitting. In some cases, however, only one case could be tested on a particular day.

The investigator arranged with the ward staff to keep the subjects fasting and rested overnight on the night preceding the day of testing.

Between 6:45 to 7:00 on the first test day a Vasocan Braunüle was inserted in to a vein in the cubital fossa. The cannule allows for repeated procedures to be performed without repeating venesection. The cannule was fixed to the arm with plaster. In cases where there was reason to believe that the patient might try to remove the cannule, the sleeve of the person's clothing was rolled down over the cannule and fixed to the wrist with plaster. In most cases the cannule did not seem to bother them if they could not see it.

One hour after insertion of the cannule blood was taken for basal T4, TSH and prolactin levels. The total volume of blood collected was three ml. Baseline cortisol levels were also determined using these samples.

At 8:00 proterilin (TRH) 200 μg was administered intravenously over a period of 30-60 seconds. The blood pressure was measured before administration and at five-minute intervals thereafter until 15 minutes after administration of the proterilin.

As the peak TSH response was expected between 20 and 30 minutes after the administration of TRH, the blood samples were collected after 20, 40 and 90 minutes for TSH levels. Two ml of blood was collected per sample. (The total volume of blood collected during these procedures was nine ml.) The samples were transported at room temperature to the laboratory.

The braunules were removed after the last sample had been collected and the patients then received a late breakfast.

6.2.4.2 *Procedure for the dexamethasone suppression test*

One day prior to the test, the investigator arranged with the ward staff to have the subjects available in the ward at the designated times; supplied the dexamethasone in sealed envelopes to the professional nurse in charge of the ward and prescribed the drug on the subjects' prescription charts.

At 23:00 of the day preceding the test, the patient received one mg of dexamethasone orally.

Blood for the determination of cortisol levels were collected at 8:00, 16:00 and 23:00 respectively on the following day. Two ml of blood was collected per sample. (The total volume of blood collected on the second day was six ml.)

In all cases, the TRHST was performed before the dexamethasone suppression test. The order in which the tests are performed, is important because dexamethasone will cause suppression of the TRH response.

The Biochemistry laboratory at the Universitas Hospital determined all blood levels. Immunoassays were performed using the chemi-luminescence test (Bayer ACS 180). Individual tests took 15 minutes to perform for the first sample analysed plus one minute per each extra blood sample analysed.

6.2.5 Statistical Analysis

Within each group (aggressive and non-aggressive), continuous variables were described by means and standard deviations or means and percentiles as applicable. Categorical variables were described by frequencies and percentages. Blood results were categorised according to normal values and described by frequencies and percentages. In the case of cortisol, the cut-off values for non-suppression was 140 nmol/L. In the case of the 8:00 sample the cut-off point of 50nmol/L was also used (as is done in the screening test for Cushing syndrome). The cut-off point for baseline TSH was < 5 μU/ml and a blunted response was regarded as delta max TSH <5 (Loosen & Prange, 1982: 408), > 20 μU/ml. An alternative cut-off point for delta max of <7 was also investigated (Nemeroff, 1989:14).

The normal range for baseline cortisol levels is 118.6 – 618.0 nmol/L (4.30–22.40μg/dl) (Product information, Bayer). Baseline prolactin levels were categorised according to standard laboratory cut-off values as follows: Premenopausal females: 59–619μIU/ml; Postmenopausal females: 38–430 μIU/ml; and males 45–375μIU/ml. The standard range for T4 is 11–22 pmol/l. The two groups were compared with regard to baseline levels by means of the Wilcoxon test and 98.3 % confidence intervals for paired data.

Within each group, the change from baseline for TSH and cortisol was calculated, while the changes between the groups were assessed by the Wilcoxon test and 98.3 % confidence intervals for paired data.

The median baseline prolactin levels for patients on thioridazine were compared with those of patients on other medication by the Mann Whitney test and a 95 % non-parametric confidence interval for the median difference. The confidence interval was interpreted for clinical relevance.

Spearman's rank correlation coefficient was calculated between age and baseline cortisol values. Subjects with mild intermittent aggressive episodes were classified as having normal or elevated baseline cortisol levels. The percentage subjects in the groups were compared by 95 % Wilson confidence intervals.

In all statistical tests an alpha level of 0.05 was used.

6.2.6 Measurement and Methodology bias

Due to practical reasons subjects on antipsychotic treatment could not be pharmacologically dried out for the procedure. Prolactin levels were used to assess the possible effect of the antipsychotic on hypothalamic function.

6.2.7 Summary of procedures

The dexamethasone suppression test was performed on a total of 55 subjects and the thyroid–releasing hormone stimulation test on a total of 57 subjects (including 2 subjects in the pilot study).

6.2.7.1 *Drop outs*

- J.K. male, change in level of functioning of matched aggressive subject, no substitute could be found.
- J.M. 55-year-old male, change in level of functioning of matched aggressive subject, no substitute could be found.

- A.B. 41-year-old male, change in level of functioning of matched aggressive subject, no substitute could be found.
- C.V. 58-year-old male, wrongfully selected, subject on carbamazepine.
- P.M. 49-year-old male, wrong selection, subject on reserpine.
- A.S. 24-year-old male, wrong selection, behaviour not aggressive.
- P.S. 53-year-old male, match was cancelled due to incomplete consent from guardians.
- P.N. 33-year-old male, change in level of functioning of matched subject, no substitute could be found.
- N.M. 25-year-old male, matched subject was rejected, see A.S.
- One matched female pair, M.M. (36) and L.M. (28), was excluded due to a difference in functioning level.

6.2.7.2 *Adverse effects*

No serious adverse events occurred during the procedures. Transient changes in blood pressure were the only side effect that occurred in two patients. In both patients the adverse event resolved spontaneously within 15 minutes without any sequelae.

- Subject E.M.: A 23-year-old female patient experienced a drop in blood pressure from 110/70 to 80/50 directly after the administration of proterilin. The patient was in the recumbent position throughout the procedure and did not show any signs of distress. The blood pressure was monitored every five minutes and recovered spontaneously within 15 minutes.

- Subject A.B.: A 43-year-old female patient experienced a transient elevation of blood pressure from 130/80 at baseline to 150/110 after five minutes. The blood pressure came down to 140/100 at 10 minutes and stabilised at 130/80 after 15 minutes.

6.3 CONCLUSION

The DST was relatively easy to perform and also required a relatively low level of co-operation if compared to the TRHST. As the TRHST was performed before the DST, the subjects who were able to co-operate in the TRHST were also able to co-operate in the DST.

The TRHST was generally well tolerated by the subjects, although several prospective subjects had to be excluded because sufficient co-operation could not be obtained. Adverse events were few and transient.

The results of the study will be reflected in Chapter 7. A summary of the raw data can be found in the Appendix.

CHAPTER 7
RESULTS

7.1 GENERAL PROFILE

The results of 44 subjects (26 males and 18 females) were included in the final analysis. The group consisted of an aggressive (n=22) and non-aggressive (n=22) group, each consisting of 13 males and nine females. The groups were matched according to gender, age (within 10 years), and level of functioning. The mean age of the aggressive group was 44.1 years (±SD 9.8), while the mean age of the non-aggressive group was 44.2 years (±SD 10.5). Two pairs were profoundly mentally retarded, 17 pairs severely mentally retarded and three pairs were moderately mentally retarded. No associated symptoms were found in 59.1 % (13) of the aggressive subjects; 9.1 % (two) were reported to have sleep disturbance; 13.6 % (three) had libido disturbances; 9.1 % (two) showed signs of psychosis; 4.6 % (one) had manic episodes; and 4.6 % (one) had both sleep and libido disturbances.

Table 7.1: Antipsychotic drug use in the aggressive group

Drug	Frequency		Percentage	
n=22	**First drug**	**Second drug**	**First drug**	**Second drug**
Thioridazine	13	1	59.1 %	4.5 %
Clozapine	3	0	13.6 %	0 %
Zuclopentixol	2	1	9.1 %	4.5 %
Haloperidol	2	0	9.1 %	0 %
Other	2	4	9.1 %	18.2 %
Total	**22**	**6**	**100 %**	**27.3 %**

The median duration of uninterrupted drug use was 24 months with an interquartile range of 17-42 months.

7.2 BEHAVIOUR ASSESSMENT

Table 7.2 reflects the type and pattern of aggression as derived from information provided by the ward staff and the hospital notes.

Table 7.2: Type of behaviour, degree and frequency

Type of behaviour	**Total Number** n=22	**Degree**	**Frequency**
Self-injury	6 (27.3 %)	1 Mild (4.5 %)	Intermittently
		5 Moderate (22.7 %)	1 intermittently
			4 daily
Verbal aggression	7 (31.8 %)	2 provoked (9.1 %)	1 weekly to monthly
			1 intermittently
		5 unprovoked (22.7 %)	1 daily
			3 weekly to monthly
			1 intermittently
Physical aggression directed at others	17 (77.3 %)	11 mild (50 %)	2 daily
			1 weekly to monthly
			8 intermittently
		3 moderate (13.6 %)	1 daily
			1 weekly to monthly
			1 intermittently
		3 severe (13.6 %)	1 weekly to monthly 2 intermittently
Physical aggression directed at property	4 (18.2 %)	1 mild (4.5 %)	Daily
		2 moderate (9.1 %)	1 Daily
			1 intermittently
		1 severe (4.5 %)	Weekly to monthly

7.2.1 Combinations of behaviour

The combination of physical aggression and verbal aggression occurred in five subjects (22.7 %) and a combination of self-injury, physical aggression towards others and verbal aggression in one subject (4.5 %).

7.2.2 Activity

Activity was assessed through evaluating the incident free period prior to testing, the necessity to apply additional measures to control behaviour, and recording the occurrence of aggressive incidents during a four-week period.

From the hospital notes it was determined that 12 (54,5 %) of the aggressive subjects (n=22) had showed aggressive activity during the month preceding testing. In three cases (13,6 %) the last reported incident occurred between two and six months prior to testing and in one case (4,5 %) the last incident occurred between six and 12 months earlier. In six cases (27,3 %) the last incident was recorded between 12 and 45 months previously.

A second drug was used in six subjects (27.3 %), behaviour modification was used in three subjects (13.6 %) and restraint measures were used in four cases (18.2 %). (The restraint measures involved the use of bandages to prevent self-injury.)

The following table summarises the results of the incidents reported during the four-week observation period.

Table 7.3: Aggressive episodes during the observation period

	Number of incidents			
Number of subjects n=11	**Self-injury**	**Verbal aggression**	**Aggression directed at property**	**Aggression directed at other persons**
3	0	0	0	1 mild
	0	0	0	1 mild
	0	0	0	1 mild
3	moderate, daily	0	0	0
	mild, daily	0	0	0
	mild, daily	0	0	0
2	0	0	Daily, severe	0
			6 moderate	
1	0	6 unprovoked	0	3 moderate
1	1 mild	2 provoked	0	1 mild, 3 moderate
1			4 mild, 2 moderate	1 mild

A subject was regarded as having recent aggressive activity if any aggressive activity had been recorded during the observation period, if there had been a record of aggressive activity within six months prior to the study, or if restraint measures had to be employed to prevent injury. According to this definition, there were 15 subjects (68 %) in the aggressive group with recent aggressive activity.

7.3 EVALUATION OF HYPOTHALAMIC-PITUITARY-ADRENAL AXIS FUNCTION

The hypothalamic-pituitary-adrenal axis function was assessed by measuring baseline cortisol levels as well as by the performance of the dexamethasone suppression test. The baseline cortisol level may indicate over-activation of the HPA axis, yet is fairly non-specific, while the DST can determine more subtle abnormalities of the axis that is highly specific for major depression.

7.3.1 Baseline cortisol levels

The baseline cortisol level was determined on the baseline sample collected before the administration of proterilin.

Table 7.4: Baseline cortisol levels

	Median values (interquartile range) (nmol/L)	
	Aggressive	**Non-aggressive**
Cortisol	496.5 (381; 609)	410.5 (337; 516.0)

The baseline cortisol level in the aggressive group was higher than in the non-aggressive group. The difference is not statistically significant, yet it is of clinical relevance.

Table 7.5: Comparison between the two groups regarding baseline cortisol levels

	Median difference: Aggressive– non-aggressive [CI]	**Wilcoxon signed rank p-value**
Cortisol (nmol/L)	101 [-70; 209]	0.14

[CI]: 95 % Non-parametric confidence interval for the median paired difference.

7.3.1.1 *Abnormal baseline cortisol levels*

There were five subjects in the aggressive group with elevated baseline cortisol levels and two subjects in the non-aggressive group with elevated baseline cortisol levels. No subjects in either group were found with abnormally low baseline cortisol levels.

7.3.1.2 *Possible determinants of elevated or high baseline cortisol levels*

The possibility of a correlation of elevated baseline cortisol levels with age; the type of behaviour; and the presence of mild intermittent episodes of aggression were investigated.

Table 7.6: Baseline cortisol levels vs. age

Aggressive group

Median age (interquartile range)		
Normal baseline cortisol (n=17)	Elevated baseline cortisol (n=5)	Kruskal-Wallis p-value
45 (35; 53)	44 (41; 48)	0.87

No correlation (Spearman r =0.09) was found between age and baseline cortisol.

Non-aggressive group

Median age (interquartile range)		
Normal baseline cortisol (n=20)	Elevated baseline cortisol (n=2)	Kruskal-Wallis p-value
44.5 (38.5; 53)	40.5 (31; 50.0)	0.52

No correlation (Spearman r =-0.19) was found between age and baseline cortisol.

The difference between the ages of those with normal baseline cortisol levels and those with elevated baseline cortisol levels was statistically insignificant.

Table 7.7: Number of subjects with normal baseline cortisol levels and elevated baseline cortisol levels exhibiting different types of behaviour

	Normal baseline cortisol	**Elevated baseline cortisol**
Self-injurious behaviour	5	1
Verbal aggression	5	2
Physical aggression directed at other persons	12	5
Physical aggression directed at property	3	1

Table 7.8: Subjects with mild intermittent aggressive episodes: Comparison between group with normal baseline cortisol levels and group with elevated baseline cortisol levels

Mild intermittent episodes with normal baseline cortisol levels (n=12)	**Mild intermittent episodes with elevated baseline cortisol levels** (n=5)	**Difference** (Elevated – normal) [Wilson CI]
4 (33.3 %)	4 (80 %)	46.7 % [-4 %; 72.1 %]

The difference between the percentage of subjects with mild intermittent episodes regarding baseline cortisol levels is not statistically significant (95 % Wilson confidence interval [-4 %; 72.1 %]). The uncertainty of the estimation that is reflected by the wide confidence interval is due to the limited number of subjects. However, there is a tendency towards a higher percentage of subjects with elevated baseline cortisol levels having mild intermittent episodes than the percentage of subjects with normal baseline cortisol levels.

If an arbitrary cut-off point of 500 nmol/L is used for baseline cortisol levels, the following picture is seen:

Table 7.9: Comparison of number of subjects with high baseline cortisol levels with aggressive activity in the aggressive group

	Subjects with recent aggressive activity	Subjects with no recent aggressive activity
Baseline cortisol level ≥ 500 nmol/L (n=11)	9 (81.8 %)	2 (18.2 %)
Baseline cortisol level < 500 nmol/L (n=11)	6 (54.5 %)	5 (45.5 %)

The group with higher baseline cortisol levels tended to show more recent aggressive activity than the group with lower cortisol levels, although the difference is not statistically significant with a Chi-square p=0.36 and a 95 % Wilson confidence interval for the difference in prevalence of [-5.3 %; 53 %].

7.3.2 The dexamethasone suppression test

The dexamethasone suppression test was performed after the administration of one mg of dexamethasone at 23:00 on the night prior to the test.

Table 7.10: Cortisol levels during DST

	Median values (Interquartile range) (nmol/L)	
	Aggressive	**Non-aggressive**
8:00	25.4 (20.8; 45.3)	20.4 (16.9; 36.5)
16:00	18.8 (13.2; 25.1)	18.9 (12.7; 28.5)
23:00	9.4 (5.8; 21.5)	12.8 (5.9; 35)

Table 7.11: Cortisol change from baseline

	Median values (Interquartile range) (nmol/L)	
	Aggressive	**Non-aggressive**
Baseline- 8:00	446.5 (349.6; 549.6)	372.6 (314.5; 470.9)
Baseline- 16:00	471 (361.1; 593.1)	393.3 (312.1; 462.5)
Baseline- 23:00	447.1 (343.4; 601.1)	392.9 (312.4; 456.8)

Table 7.12: Comparison of difference in change from baseline

	Median change (Interquartile range) Non-aggressive-aggressive	**Wilcoxon signed rank p-value**
Baseline- 8:00	-79.2 (-198.5; 71.9)	0.22
Baseline- 16:00	-99.5 (-201.7; 62.2)	0.11
Baseline- 23:00	-104 (-209.4; -85.7)	0.12

The changes from baseline to 8:00, 16:00 and 23:00 were larger in the aggressive group than in the non-aggressive group and the gap widened progressively with time. The difference in change is not statistically significant.

Table 7.13: Categorisation of cortisol suppression

Sample	Value range (nmol/L)	Number of subjects	
		Aggressive group n=22	**Non-aggressive group** n=22
8:00	<140	21 (95.5 %)	21 (95.5 %)
	>=140	1 (4.5 %)	1 (4.5 %)
	<50	18 (81.8 %)	21 (95.5 %)
	>=50	4 (18.18 %)	1 (4.5 %)
16:00	<140	22 (100 %)	21 (95.5 %)
	>=140	0 %	1 (4.5 %)
23:00	<140	21 (95.5 %)	22 (100 %)
	>=140	1 (4.5 %)	0 %

The total number of subjects with non-suppression below the cut-off point of 140 nmol/L does not differ between the two groups, yet there is a marginally larger aggressive group with non-suppression of the 8:00 level below 50nmol/L.

Table 7.14: Abnormal baseline cortisol vs. cortisol non-suppression

Aggressive group

	Cut-off point 140 nmol/L at 8:00, 16:00 or 23:00	**Cut-off point 50 nmol/L at 8:00**
Normal baseline cortisol (n=17)	1 (5.9 %) non-suppression at 23:00 16 (94.1 %) normal DST	2 (11.8 %) > 50 15 (88.2 %) < 50
Elevated baseline cortisol (n=5)	1 (20 %) non-suppression at 8:00 4 (80 %) normal DST	2 (40 %) >50 at 8:00 3 (60 %) <50 at 8:00

Non-aggressive group

	Cut-off point 140 at 8:00, 16:00 or 23:00	**Cut-off point 50 at 8:00**
Normal baseline cortisol (n=20)	1 (5 %) non-suppression at 8:00, 16:00 19 (95 %) normal DST	1 (5 %)> 50 at 8:00 19 (95 %) < 50
Elevated baseline cortisol (n=2)	2 (100 %) normal DST	2 (100 %) < 50

Non-suppression at cut-off point 140nmol/L for all samples or 50nmol/L for the 8:00 sample is not related to an elevated baseline cortisol.

7.4 EVALUATION OF HYPOTHALAMIC-PITUITARY-THYROID AXIS FUNCTION

The hypothalamic-pituitary-thyroid axis function was evaluated through the determination of baseline T4 and TSH levels and the performance of the thyroid-releasing hormone stimulation test. Baseline prolactin levels were measured to determine the influence of the antipsychotic drugs used by the aggressive group.

7.4.1 Baseline assessment of prolactin, TSH and T4

All baseline levels were determined on a single blood sample collected before the administration of proterilin and one hour after the insertion of the intravenous cannule.

Table 7.15: Baseline levels of prolactin, TSH and T4

	Median baseline values (Interquartile range)	
	Aggressive	**Non-aggressive**
Prolactin (μIU/ml)	386 (239; 632)	178 (146; 212)
TSH (μU/ml)	1.7 (1.32; 2.26)	1.7 (1.0; 3.4)
T4 (pmol/l)	13.7 (13.1; 14.5)	13.6 (12.7; 15.2)

Table 7.16: Comparison between the two groups regarding baseline levels of prolactin, TSH and T4

	Median difference: Aggressive– non-aggressive [CI]	**Wilcoxon signed rank p-value**
Prolactin (μIU/ml)	220.5 [31; 469]	0.0003
TSH (μU/ml)	0.14 [-0.5; 0.98]	0.58
T4 (pmol/l)	0.1 [-1.9-1.5]	0.95

[CI]: 95 % Non-parametric confidence interval for the median paired difference.

The baseline prolactin values were higher in the aggressive group than in the non-aggressive group, which is clinically relevant, yet not significant according to the CI.

The baseline TSH values were slightly higher in the aggressive group than in the non-aggressive group, but the difference is not statistically or clinically significant.

7.4.1.1 *Abnormal baseline levels of prolactin, TSH and T4*

- BASELINE PROLACTIN

An elevated prolactin level occurred in 11 aggressive subjects (50 %), while there were no abnormal values recorded in the non-aggressive group. This was an expected result due to the dopamine antagonistic effect of the antipsychotic drugs that inhibits the effect of prolactin inhibiting factor. Ten of the 14 subjects (71.4 %) on thioridazine had an increased prolactin level, while only one of the eight subjects (12.5 %) on other antipsychotic drugs had elevated prolactin levels.

- BASELINE TSH

The baseline TSH level of one subject in the aggressive group (4.5 %) was more than 5 μU/ml. Baseline TSH levels of more than 5 μU/ml occurred in two subjects (9.1 %) in the non-aggressive group.

- BASELINE T4

A T4 level of less than 11 pmol/l occurred in one subject (4.5 %) in the aggressive group. This individual had a normal THRST.

Table 7.17: Comparison of prolactin levels of subjects on thioridazine and subjects on other antipsychotics

Median prolactin levels (interquartile range) μIU/ml n=22			
Thioridazine 14 subjects (63.6 %)	Other antipsychotics 8 subjects (36.4 %)	Difference (Thioridazine – rest) [CI]	p-value (Mann-Whitney)
589 (262; 1220)	230.5 (111; 348)	329[123; 864]	0.01

CI: 95 % Non-parametric confidence interval

The difference between the median baseline prolactin values of subjects on thioridazine and subjects on other drugs is statistically significant according to both the p-value and the 95 % non-parametric confidence interval for the median difference (thioridazine-rest).

7.4.2 The thyroid-releasing hormone stimulation test

Table 7.18 reflects the TSH values found in the two groups with the TRHST.

Table 7.18: TSH levels during TRHST

	Median TSH (Interquartile range) (μU/ml)	
	Aggressive (n=22)	**Non-aggressive** (n=22)
Baseline 8:00	1.7 (1.3; 2.6)	1.7 (1; 3.4)
8:20	12.3 (10.2; 14.8)	12.3 (7.6; 19.1)
8:40	11.1 (7.7; 20.6)	11.1 (7.8; 20.6)
9:30	6.9 (5.4; 9.2)	6.7 (4.6; 11.6)

There are minimal differences in the median TSH values of the two groups.

Table 7.19: Comparison of the area under the curve TRHST

	Median AUC (Interquartile range)
Aggressive (n=22)	852.1 (668.7; 995.5)
Non-aggressive (n=22)	820 (567.2; 1430.3)
Difference: Aggressive – non-aggressive	8.48 (-363.3; 287.8)

The difference in the area under the curve between the two groups is not statistically significant (Wilcoxon signed rank p=0.65).

Table 7.20: Comparison of Delta C (change from baseline) TSH in the two groups

	Median Delta C TSH (Interquartile range) (μU/ml)	
	Aggressive (n=22)	**Non-aggressive** (n=22)
8:20-8:00	11.1 (8.4; 12.2)	10.6 (6.7; 16.7)
8::40-8:00	9.6 (7.6; 12.5)	9.4 (6.8; 15.1)
9:30-8:00	5.1 (3.7; 7.0)	5.1 (3.9; 8.8)

Table 7.21: Difference in Delta C (change from baseline) TSH between the two groups

	Non-aggressive – Aggressive Median change from baseline (Interquartile range) (μU/ml)	**Wilcoxon p-value**
8:00-8:20	1.53 (-3.46; 4.25)	0.49
8:00-8:40	0.54 (-2.14; 6.95)	0.36
8:00-9:30	0.17 (-2.54; 3.04)	0.64

The difference in change from baseline between the two groups is statistically insignificant.

Table 7.22: Categorisation of TSH response

C max Value range (μU/ml)	Number of subjects	
	Aggressive group (n=22)	Non-aggressive group (n=22)
<7	2 (9.1 %)	6 (27.3 %)
7-20	19 (86.4 %)	13 (59.1 %)
>20	1 (4.5 %)	3 (13.6 %)
<5	2 (9.1 %)	0 %
5-20	19 (86.4 %)	19 (86.4 %)
>20	1 (4.5 %)	3 (13.6 %)

The non-aggressive group tended to show more persons with a blunted response if the cut-off value of 7 μU/ml was used. There were also more individuals in the non-aggressive group with an exaggerated response.

7.5 CONCLUSION

The study shows a difference in the baseline cortisol levels of the two groups which is not statistically significant, but is of clinical relevance (see Tables 7.4 and 7.5). A higher percentage of subjects with elevated baseline cortisol levels exhibited continued mild intermittent episodes of aggression (see Table 7.8) and there is a tendency for individuals with recent aggressive activity to have higher baseline cortisol levels (see Table 7.9). Non-suppression of cortisol occurred in both groups (See Table 7.13). Four individuals in the aggressive group showed cortisol levels at 8:00 of more than 50 nmol/L.

Although there was no difference in the median TSH values (see Table 7.18) and the median area under the curve (see Table 7.19), definitive HPT axis abnormalities occurred in the form of a blunted TSH response in two (9.1 %) individuals in the aggressive group (n=22). The study also revealed the

presence of subclinical hypothyroidism in three individuals and the presence of primary hypothyroidism in one female subject in the non-aggressive group (see Table 7.22 and Appendix: subject 409).

Secondary findings are the demonstration of the continued popularity of the typical antipsychotic drugs for the treatment of aggressive and self-injuring behaviour (see Table 7.1) and the effect of thioridazine on prolactin levels (see Table 7.15).

The results and findings of the study will be discussed and recommendations regarding practical implications proposed in Chapter 8.

CHAPTER 8
DISCUSSION AND RECOMMENDATIONS

8.1 DISCUSSION

The DST was used in previous studies on mentally retarded persons (Ruedrich, Wadle, Sallach, Hahn & Menolascino, 1987; Beckwith, Parker, Pawlarczyk, Couk, Schumacher & Yearwood, 1985) as well as the determination of cortisol levels (Hessl, Glaser, Dyer-Friedman, Blasey, Hastie, Gunnar & Reiss, 2002). There were no studies on the TRHST in mentally retarded persons found in the literature. Direct comparisons are therefore not possible.

The small sample size makes the generalisation of findings problematic.

8.1.1 Baseline hypercortisolaemia

Baseline hypercortisolaemia occurred in a total of seven (15,9 %) of the 44 test subjects: five of the 22 aggressive subjects (22.7 %) and in two of the 22 non-aggressive ones (9.1 %). Ruedrich *et al.* (1987:598) found baseline hypercortisolaemia in 36 % of mentally retarded persons (n= 85). They demonstrated a correlation of both hypercortisolaemia and DST non-suppression with greater age (Ruedrich *et al.*, 1987:599). Sapolsky *et al.* (1986:280) ascribe the phenomenon of HPA activation in old age to neuronal loss in the hippocampus combined with a loss in glucocorticoid and corticosterone receptors, resulting in impaired feedback control and an inability to inhibit the hypothalamus and subsequently an inability to terminate the stress response. It is however not seen as part of the normal ageing process and only appears if there is a concomittant pathological process (Sapolsky *et al.*, 1986:296). In the present study higher cortisol levels were not related to age (see Table 7.6). This may be due to the exclusion of subjects older than 60.

In this study, baseline cortisol levels were not related to the type of aggression (see Table 7.7), yet subjects with more recent aggressive activity had higher baseline cortisol levels (see Table 7.9). Hessl *et al.* (2002:866) reported higher salivary cortisol levels in boys with fragile X syndrome. They also found that higher cortisol levels were associated with greater severity of behaviour problems.

Elevated cortisol levels are not specific for depression, yet the finding of hypercortisolaemia is significant, because it may reflect an etiologial factor in the development of behaviour problems. The hippocampus with its high concentration of glucocorticoid receptors, appears to be especially vulnerable to glucocorticoids acting as neurotoxic agents with rapid and persistent effects on the hippocampus (Sapolsky *et al.,* 1986:293). Where short-term exposure to high corticosteroid levels may have transient effects, long-term exposure may cause permanent neuronal damage to the hippocampus. The hippocampus is important in cognition (Sapolsky *et al.,* 1986:294), as well as being an important component of the limbic system that controls affect. Hippocampal damage may thus eventually result in affective dysfunction as well as deterioration of cognitive function.

8.1.2 Cortisol non-suppression with the DST

According to the classical definition, cortisol non-suppression occurred with the dexamethasone suppression test in two subjects in the aggressive group (9.1 %) and one subject in the non-aggressive group (4.5 %), totalling 6.8 % of the total group. Ruedrich *et al.* (1987:598) demonstrated non-suppression of cortisol by dexamethasone in 24 % of their research group of mentally retarded persons. Sireling (1986:277) identified one case of cortisol non-suppression in a group of 12 mentally retardates with major depression. Beckwith *et al.* (1985:828) demonstrated an overall percentage of 40 % of depressed patients in a group of 36 non-suppressor mentally retardates.

Employing an alternative cut-off point of 50 nmol/L for the 8:00 sample (as used in the DST screening test for Cushings), yielded four subjects with a level above 50 nmol/L at 8:00 in the aggressive group.

- Subject 103, a 56-year-old aggressive male with recent aggressive activity against people and verbal aggression had an elevated baseline cortisol; an 8:00 cortisol level of >50 nmol/L; followed by normal suppression at 16:00 and 23:00. In addition, the subject also exhibited a blunted TSH response in the presence of normal T4 and baseline TSH levels. His prolactin level was normal.

- Subject 104, a 55-year-old aggressive male with recent aggressive activity against people as well as verbal aggression had an elevated baseline cortisol level and an 8:00 cortisol level of > 50nmol/L, followed by normal suppression at 16:00 and 23:00. The individual had a normal TRHST with an elevated prolactin level and was on treatment with thioridazine.

- Subject 108, a 41-year-old aggressive male with no recent aggressive activity showed an elevated baseline cortisol level, initial non-suppression by dexamethasone at 8:00, followed by normal suppression. He also showed a blunted TSH response in the presence of normal T4 and baseline TSH levels.

- Subject 306, a 36-year-old female subject with recent aggressive episodes against people, had baseline cortisol levels above 500nmol/L and an 8:00 cortisol level of > 50 nmol/L, followed by normal suppression at 16:00 and early escape at 23:00. The TRHST was normal.

The particular combination of a high or elevated baseline cortisol level and escape from suppression or partial suppression at 8:00 did not occur in the non-aggressive group where the only individual with abnormal levels during

the DST (see Appendix subject 206) showed normal baseline cortisol levels of less than 500 nmol/L combined with non-suppression at 8:00 and 16:00. Beckwith *et al.* (1985:828) described this pattern of initial suppression, followed by early escape from suppression later in the day as the typical pattern seen in depressed mentally retardates. Carroll (1982:294) also found that 98 % of abnormal results were detected on the 16:00 and 23:00 samples, yet does not exclude the 24 % abnormalities detected on the 8:00 levels. The presence of abnormalities of the DST in the non-aggressive group is not surprising, as Beckwith *et al.* (1985:830) also postulated that there might be an alternative expression of major depression in some institutionalised mentally retardates, presenting as a quiet passivity that is mistakenly interpreted as co-operativeness.

Ruedrich *et al.* (1987:601) postulated that activation of the hypothalamic-pituitary-adrenal axis, as reflected by hypercortisolaemia and/or non-suppression, could be explained by the presence of an undiagnosed psychiatric disorder, namely major depressive disorder, unapparent because of the retardation of the subjects. Aggression may thus reflect psychomotor agitation and behavioural manifestations of affective dysfunction in mental retardation. It is, however, possible that chronic hypercortisolaemia due to either ineffective termination of the stress response or over-activation of the HPA axis may cause depressive symptoms, as demonstrated by glucorticosteroid use and in Cushing syndrome. Depression may thus only be one of the possible manifestations of a hyperactive state of the HPA axis.

8.1.3 Blunted TSH response with TRHST

TSH blunting is not specific to depression and also occurs in some patients with mania, anorexia nervosa and alcoholism. It does however, not occur in schizophrenia (Loosen & Prange, 1982:408). None of the patients showing TSH blunting in the present study had any of the three conditions mentioned. The significance of blunting is not clear, but in some patients it develops after prolonged depression. Kirkegaard *et al.* (1975:1118) postulated that elevated

plasma cortisol levels may be the cause of a blunted response to TSH. However, according to Loosen and Prange (1982:410), it is doubtful whether adrenal activation accounts for the TSH blunting, and either reduced serotonergic input or increased noradrenaline input leads to a hypersecretion of TRH. The initial response is an increase in TSH secretion, but ultimately the pituitary becomes hyporesponsive due to down-regulation of receptors (Loosen & Prange, 1982:411).

The occurrence of a blunted TSH response in combination with HPA axis abnormalities in two of the subjects in the aggressive group supports the diagnosis of depression or in the absence of clinical symptoms rather to be called a neurochemical disturbance similar to that found in major depression. It also supports a role for elevated cortisol levels as a possible etiological factor.

The prevalence of blunted TSH response in the aggressive group (9.1 %) is much lower than the 25 % non-suppression reported by Loosen *et al.* (1983:702) and numerous other studies done on persons with major depression (Nemeroff, 1989:16), using the cut-off point of 5 μU/ml for maximum delta TSH. Other studies, however, used a higher cut-off value of 7 μU/ml (Loosen & Prange 1982:408). With this higher value defining the fault, six additional subjects in the non-aggressive group also exhibited a blunted TSH response, in total eight (18.2 %) of the total study group (n=44). As these subjects were all asymptomatic and there were no accompanying abnormalities of the HPA axis, the cut-off point of 5 μU/ml was regarded as the valid value.

8.1.4 Hyperprolactinaemia

An elevated prolactin level occurred in 11 subjects in the aggressive group (50 %). Subjects on thioridazine were particularly likely to exhibit an elevated prolactin level (see Table 7.17). The effect can be explained by the dopamine antagonistic action of the antipsychotic drugs on the pituitary. Dopamine is known to inhibit the secretion of both TSH and prolactin. As the elevated prolactin levels reflect dopamine inhibition, it may be that the higher prolactin levels may actually mask a blunted response by causing higher TSH levels.

8.1.5 Exaggerated TSH response with the TRHST

One female subject (409) in the non-aggressive group exhibited a combination of an elevated baseline TSH and an exaggerated TSH response. This constitutes a diagnosis of primary hypothyroidism. An exaggerated TSH response in the presence of normal thyroid hormone levels and normal baseline TSH levels occurred in two female patients in the non-aggressive group and one male patient in the aggressive group, indicating subclinical hypothyroidism. Kraus, Phoenix, Edmonds, Nicholson, Chandarana and Tokmakejian (1997:268) found 38 % prevalence (n=60) of exaggerated TSH response (> 25) in a group of depressed patients with normal TSH screening levels. Subclinical hypothyroidism is a mild form of hypothyroidism. Hypothyroidism is routinely excluded before the diagnosis of depression is made. Depression associated with hypothyroidism does not respond well to antidepressants, unless thyroid hormone replacement is instituted as well. The higher prevalence in the non-aggressive group may be explained by an alternative expression of depression in these patients (Beckwith *et al.* 1985: 830).

8.1.6 Antipsychotic drug use

The study demonstrates the continued popularity of antipsychotic drugs as first-line therapy for aggression and self-injuring behaviour. Thioridazine is by far the most popular choice in this group (63.6 %). There were only three subjects (13.6 %) in this particular study group who were treated with an atypical antipsychotic as a first drug, namely clozapine.

The profile can be explained by the cost of atypical antipsychotics and the unavailability in state institutions. The popularity of thioridazine can be ascribed to its favourable side effect profile, especially with regard to extra-pyramidal side effects. The drug was, however, recently pointed out as the antipsychotic that is most commonly associated with QT prolongation and sudden death (Glassman & Bigger, 2001:9 of 13).

8.2 RECOMMENDATIONS

The mentally retarded person may be unable to give meaningful expression to depression. It is therefore a reasonable assumption that depression, or a neuro-endocrine equivalent thereof, may be undetected in such an individual due to absent, subtle or altered behavioural expression of the disease. Given the high specificity of the DST of 96 % for major depression (Carroll, 1982:294), it is reasonable to speculate that an abnormal DST, even in the absence of overt symptomatology, may be due to an underlying depressive equivalent that may respond to antidepressant therapy. Carroll (1982:296) recommends in this regard that "an abnormal DST result is a definitive indication for some form of somatic antidepressant treatment" on the grounds that an abnormal DST may in fact precede the onset of clinically detectable depression (Carroll, 1982:297).

The question remains whether a high baseline cortisol without other evidence of HPA axis activation should be manipulated and whether normalisation of the cortisol level will indeed improve aggressive and/or self-injuring behaviour. Baseline hypercortisolaemia shows a specificity for major depression of only

55 % (Carroll, 1982:295). Yet these individuals may indeed have an undetected depression. Given the detrimental effects of long-term elevation of cortisol, a trial of antidepressant therapy should be considered. As the HPA axis is predominantly dependent on serotonergic input, a serotonergic antidepressant seems a logic choice.

Cortisol non-suppression is well known to normalise after successful treatment of depression (Nemeroff 1989:17). Kirkegaard *et al.* (1975:1118) demonstrated that TSH response is increased after recovery from major depression, signifying that the HPT axis also normalises after successful treatment. According to Loosen and Prange (1982:410), there are, however, cases where the blunted response persists after recovery. The failure of recovery of the axis predicts the occurrence of relapse.

Longitudinal studies are needed to determine the relationship of baseline cortisol measurement and behaviour and its possible role as a monitoring tool during therapy.

8.3 CONCLUSION

The mentally retarded person exhibits an inherent inability to adapt to the social and physical environment. The institutionalised mentally retarded person, separated early from his family, often has to cope within the confines of scaled-down physical environment, yet sometimes very volatile and unpredictable social environment. Ironically, it seems as if the aggressive individual may be the one with less adaptive ability in terms of HPA axis function. Effective prevention of aggressive acts may provide better options for the affected individual in terms of social activities and even habilitation. The main benefit of successful management of aggression is, however, the creation of a stable social environment as an important aspect of a truly therapeutic environment.

Although the findings of the study are essentially negative, the study did show that neuro-endocrine axis abnormalities may occur undetected in low functioning mentally retarded patients. In particular, HPA axis abnormalities tend to be more prevalent, but not exclusive, among aggressive individuals. On the other hand, the behaviour of a placid, withdrawn patient may mistakenly be interpreted as normal, hiding overt or subclinical hypothyroidism.

Current developments in antidepressant therapy in the form of CRF antagonists and glucorticosteroid blockers may open new possibilities in distinguishing the exact locus of pathology in HPA axis abnormalities. The possibility of manipulating the HPA axis via oxytocin may also be a useful line of investigation (Courtney De Vries, 2002:410). In the meantime, various currently available antidepressants, including the SSRIs, have been shown to restore neurogenesis in the atrophic hippocampus demonstrated in patients with depression, most likely secondary to HPA axis activation (Duman, Nakagawa & Malberg, 2001:837).

Many questions remain unanswered. Are neuro-endocrine axis abnormalities the cause of aggressive activity in some individuals or are they incidental concommitants? Will manipulation of a neuro-endocrine axis bring about an improvement in behaviour in these individuals? Can neuro-endocrine axis abnormalities predict aggressive activity or a tendency to develop aggressive behaviour? Can the management of aggression become pro-active rather than reactive?

The answers to these questions can only be provided through continued research. The necessity of research in this field is undeniable, even in the face of ethical debate. As a vulnerable population, mentally retarded persons should be protected, yet the exclusion from research on their unique problems may also be seen as an ethical transgression, especially in the light of rapid technological and therapeutic advances in other fields of medicine. The legacy of being left behind is evident in the current approach to aggression and self-injurious behaviour in mentally retarded persons.

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LIST OF TERMINOLOGY

1. Aggression

The term was used in this study to indicate inappropriate behaviour that is aimed at causing injury to another person or to the person him-/herself; to cause damage to property; or the verbal expression of negative emotion in a violent and uncontrolled manner.

2. Self-injuring behaviour

An intentional act that results in organ or tissue damage to the individual performing the act.

3. Mental retardation

According to the DSM IV, the following conditions must be met for the diagnosis of mental retardation:

- An IQ of 70 or below
- Deficits in adaptive functioning
- Onset of the disability before the age of 18

The following levels of mental retardation are distinguished:

- Mild mental retardation: IQ more or less 50-55 to 70
- Moderate mental retardation: IQ more or less 35-40 to 50-55
- Severe mental retardation: IQ of more or less 20-25 to 35-40
- Profound mental retardation: IQ less than 20

For the sake of clarity, the term "mental retardation" is used throughout this dissertation to describe the particular population, except in the few instances where an alternative term was used in the original reference source. The use of the term is in line with the American Association of Mental Retardation and the popular use of the term in current medical literature, including both journals and textbooks.

The term "mental retardation" is regarded as offensive in the United Kingdom, where the terms "intellectual disability" and "learning disability" are used as equivalents (Fraser, Sines & Kerr,1998:1).

4. Dual diagnosis

The co-existence of mental retardation and mental illness.

5. Biological marker

This is a biological entity that is used to identify the presence of a condition or a tendency towards a condition. It may either be a state marker or a trait marker.

- State marker: A biological marker that indicates the presence of a condition. The state marker will not be present if the condition is not present and will revert to normal if the condition is treated.
- Trait marker: The marker signifies the presence of a genetically determined characteristic. The marker will be present whether the condition is active or dormant.

6. Stress response

A set of integrated responses to a hostile environment (aversive stimuli or stressors) involving multiple organ systems. The objective of the stress response is to increase the probability of survival (Carrasco & Van de Kar, 2003:236).

7. Hypothalamic-pituitary–adrenal axis

The hypothalamic-pituitary-adrenal axis is the primary system responsible for regulating and integrating the stress response. The hypothalamus controls the release of ACTH by the anterior pituitary, which, in turn, regulates the release of glucocorticosteroids by the adrenal gland. The glucocorticosteroids not only play an important part in energy metabolism, immune response and brain function – including memory and learning which underlies behavioural responses – but also regulate the HPA axis through termination of the stress response via its negative feedback action on the hypothalamus and pituitary.

8. Dexamethasone suppression test

The dexamethasone suppression test was originally designed to demonstrate HPA axis activation in patients with Cushing's syndrome. The original overnight test involves the measurement of cortisol levels at 8:00 after administration of dexamethasone at 23:00 the previous night. The test was adapted for use in psychiatric diagnosis by Carroll by the addition of cortisol measurements at 16:00 and 23:00. In a normal person the dexamethasone will lead to suppression of endogenous cortisol production and failure to do so indicates an over-activation of the HPA axis. The test, as adapted by Carroll (1982:294), has been used extensively as a biological marker in research on major depression.

9. Hypothalamic-pituitary-thyroid axis

The hypothalamic-pituitary-thyroid axis controls the production of thyroid hormones that regulate metabolism. The hypothalamus releases thyroid-releasing hormone (TRH) which is transported to the anterior pituitary. Here it binds to a specific membrane receptor on the thyrotrophs, resulting in increased synthesis of thyroid-stimulating hormone (TSH). TRH also leads to the release of prolactin as well as somatostatin. TSH is released into the general circulation and eventually binds to membrane receptors in the thyroid gland, resulting in an increase in the synthesis and release of the thyroid hormones T3 and T4. These hormones provide feedback to hypothalamic and pituitary level to control the level of TRH and TSH.

10. Thyroid-releasing hormone stimulation test

The thyroid-releasing hormone stimulation test is the most sensitive measure of the function of the HPT axis. It involves the intravenous administration of thyroid-releasing hormone (TSH), also known as proterilin, and the measurement of the resultant TSH secretion at various time intervals. The maximum response is expected between 20 and 30 minutes after administration of the proterilin. The maximum change in TSH level from baseline is an indication of the responsiveness of the axis. A blunted response has been demonstrated in major depression, alcoholism, anorexia nervosa and some patients with mania. An exaggerated response in the presence of normal thyroid hormones and baseline TSH levels has also been found in depression and represents subclinical hypothyroidism. The test is also used to distinguish between various types of hypothyroidism.

SUMMARY

Key terms: Aggression, self-injuring behaviour, mental retardation, dual diagnosis, stress response, biological marker, hypothalamic-pituitary-adrenal axis, hypothalamic-pituitary-thyroid axis, dexamethasone suppression test, thyroid-releasing hormone stimulation test.

The etiology of aggression and self-injuring behaviour in low functioning mentally retarded patients is multi-factorial and may reflect the presence of undiagnosed psychiatric conditions, unapparent due to the degree of the patient's impairment. It may also reflect hyperactivity of the stress response. The intricacies of diagnosis in this group of patients call for the development of biological markers to aid in diagnosis, therapy selection and drug response monitoring. Measuring and determining the relative contribution of individual neurotransmitters in the problem behaviour is complex and impractical.

An alternative route may be to evaluate the functions of the hypothalamic-pituitary axis, which has extensive connections with the limbic area and is relatively easy to assess. The hypothalamic-pituitary system controls the behavioural, endocrine, autonomic and immunological responses to stress. The dexamethasone suppression test (DST) as adapted by Carroll and the thyroid-releasing hormone stimulation test (TRHST) has been extensively used in research on biological markers in major depression. Stress is known to activate the hypothalamic-pituitary–adrenal (HPA) axis, reflected by elevated cortisol levels.

The study is a matched control study comparing hypothalamic-pituitary-adrenal axis function and hypothalamic-pituitary-thyroid axis function in 44 institutionalised mentally retarded patients with and without self-injuring and aggressive behaviour through the measurement of baseline cortisol levels and the application of the dexamethasone suppression test and the thyroid-releasing hormone stimulation test. The groups were matched according to gender, age and level of functioning. The mean age of the aggressive group

was 44,1 years (±SD 9,8) and the mean age of the non-aggressive group was 44,2 years (±SD 10,5).

Baseline hypercortisolaemia occurred in five of the 22 aggressive subjects (22,7 %) and in two of the 22 non-aggressive subjects (9,1 %). Cortisol non-suppression with the DST occurred in two subjects in the aggressive group (9,1 %) and one subject in the non-aggressive group (4,5 %). The DST did not demonstrate a difference in the two groups, yet there were more individuals in the aggressive group with abnormal high baseline cortisol, as well as a tendency towards a higher baseline cortisol in the aggressive group, suggesting an abnormal or more reactive stress response. Higher baseline cortisol levels were not related to age or the type of aggression, yet subjects with more recent aggressive activity showed higher baseline cortisol levels.

The TRHST was generally well tolerated by the subjects. Side effects were few and transient. There were two male subjects in the aggressive group showing a blunted TRHST. Primary hypothyroidism was demonstrated in one of the female subjects in the non-aggressive group and subclinical hypothyroidism in two subjects in the non-aggressive group, as well as in one subject in the aggressive group.

Longitudinal studies are needed to determine cortisol levels in unmedicated patients, in addition to comparing cortisol levels during different kinds of treatment.

OPSOMMING

Sleutelterme: Aggressie, selfbeserende gedrag, verstandelike vertraging, dubbele diagnose, stresrespons, biologiese merker, hipotalamus-hipofise–bynieras, hipotalamus-hipofise-tiroïedas, deksametasoononderdrukkingstoets, tiroïedvrystellingshormoonstimulasietoets.

Die etiologie van aggressiewe en selfbeserende gedrag in laag funksionerende verstandelik vertraagde pasiënte is multi-faktoriaal en mag moontlik die teenwoordigheid van ongediagnoseerde psigiatriese toestande insluit wat nie herken word nie weens die graad van die pasiënt se gestremdheid. Dit mag ook hiperreaktiwiteit van die stresrespons insluit. Biologiese merkers mag van groot waarde wees om te help met diagnose, seleksie van terapie en middelmonitering in hierdie pasiënte. Die meting van en bepaling van die relatiewe bydrae van individuele neurotransmittors tot die probleemgedrag is egter kompleks en onprakties. As ' n alternatief mag dit van waarde wees om die funksies van die hipotalamus-hipofise-as te evalueer, aangesien die as uitgebreide verbindings met die limbiese area het en relatief maklik geëvalueer kan word. Die hipotalamus-hipofisesisteem beheer die gedrags-, endokriene, outonome en immunologiese response tot stres. Die deksametasoononderdrukkingstoets (DST) soos aangepas deur Carroll en die tiroïedvrystellingshormoonstimulasietoets (TRHST) word lank reeds gebruik in navorsing oor biologiese merkers in major depressie. Dit is bekend dat stres die hipotalamus-hipofise-bynieras aktiveer, soos gereflekteer deur verhoogde kortisolvlakke.

Die studie is ' n gepaarde kontrolestudie waarin die hipotalamus-hipofise-bynierasfunksie en die hipotalamus-hipofise-tiroïedasfunksie in 44 geïnstitusionaliseerde verstandelik vertraagde pasiënte met en sonder selfbeserende en/of aggressiewe gedrag met mekaar vergelyk word. Daar word gebruik gemaak van die meting van basislynkortisolvlakke, die deksametasoononderdrukkingstoets soos aangepas deur Carroll en die tiroïedvrystellingshormoonstimulasietoets. Die groepe is gepaar met

betrekking tot geslag, ouderdom en vlak van funksionering. Die gemiddelde ouderdom van die aggressiewe groep was 44,1 jaar (±SD 9,8) en die gemiddelde ouderdom van die nie-aggressiewe groep was 44,2 jaar (±SD 10,5).

Basislynhiperkortisolemie het voorgekom in vyf van die 22 aggressiewe (22,7 %) en in twee van die 22 nie-aggressiewe proefpersone (9,1 %). Kortisol-nie-onderdrukking tydens die DST het in twee proefpersone in die aggressiewe groep (9,1 %) voorgekom en in een proefpersoon in die nie-aggressiewe groep (4,5 %). Die DST kon nie ' n onderskeid tussen die twee groepe aantoon nie. Daar was egter meer indiwidue in die aggressiewe groep met abnormale hoë basislynkortisolvlakke sowel as ' n algemene geneigdheid tot hoër basislyn kortisolvlakke in die aggressiewe groep, wat moontlik mag dui op ' n abnormale of meer reaktiewe stresrespons. Die hoër kortisolvlakke toon nie ' n korrelasie met ouderdom of die tipe aggressie nie, maar proefpersone met meer onlangse aggressiewe aktiwiteit het wel hoër kortisolvlakke getoon.

Die TRHST is oor die algemeen goed verdra deur die proefpersone. Newe effekte was min en van verbygaande aard. Daar was twee manlike proefpersone in die aggressiewe groep wat ' n afgeplatte TRHST getoon het. Primêre hipotiroïedisme het in een vroulike proefpersoon voorgekom en subkliniese hipotiroïedisme in twee proefpersone in die nie-aggressiewe groep, asook in een proefpersoon in die aggressiewe groep.

Longitudinale studies word benodig waarin kortisolvlakke in ongemedikeerde pasiënte bepaal word en gemonitor en vergelyk word tydens behandeling met verskillende modaliteite en verskillende geneesmiddels.

APPENDIX

SUMMARY OF RAW DATA: AGGRESSIVE MALES

Nr.	Age	BMI	L o F	Ass sympto ms	Long-term behaviour/ Observed behaviour over one month				IFP mnths	Drug	Duration mnths	P	T4	TRHST: TSH LEVELS					DST Cortisol levels			
					Self-injury	Verbal	Property	Persons						8:00	8:20	8:40	9:30	Cmax	Base line	8:00	16:00	23:00
101	49	18.5	Moderate	Psychosis	0/0	0/0	0/0	F1I3/0	7	CP	50	61	13.5	0.99	12.55	15.26	8.02	14.27	392	25.5	22.5	9.2
102	58	26.8	Severe	Libido	0/0	0/0	0/0	F3I1/0	20	Z	23	328	13.9	1.85	10.22	9.23	4.91	8.37	381	31.4	19.9	12.9
103	56	22.6	Severe	0	0/0	F3I2/0	0/0	F3I1/0	0	Z + T	24	262	12.7	1.32	4.16	5.29	4.51	3.97	609	59.4	41.6	41.6
104	55	21	Severe	Sleep	0/0	f1i2/0	0/0	f1i1/0	1	T	27	584	11.6	3.27	17.49	20.71	15.01	17.44	729	1050	13	2.9
105	55	25.3	Severe	0	0/0	0/0	0/0	f1i1/0	29	T	30	119	11	3.41	27.32	28.45	18.24	25.04	291	25.3	13.4	3.6
106	53	29	Severe	0	0/0	f12i2/0	0/0	f1i1/1 mild	0	FI + o	16	133	14.5	1.72	10.25	9.29	5.67	8.53	503	22.5	6.6	6.6
107	44	21	Severe	0	0/0	0/0	f3i2/cont	0/0	0	T	48	254	9.8	3.14	14.78	17.31	15.92	14.17	538	22.9	18.1	33.8
108	41	17.2	Severe	0	0/0	0/0	0/0	f1i1/0	29	T	34	239	13.3	1.07	3.1	4.26	2.92	3.19	633	272.7	39.9	21.5
109	33	34	Severe	Sleep +Libido	0/0	f2i1/0	0/0	f2i3/0	0	C	23	356	14.8	5.27	23.91	20.9	12.95	18.64	291	8.8	4.3	<5.5
110	30	21.5	Severe	Psychosis	f1i2/0	0/0	0/0	0/0	24	H	36	340	13.4	1.54	12.85	11.98	6.88	11.31	263	19	12	6.1
111	25	17.3	Severe	Libido	0/0	0/0	0/0	f1i1/0	45	T	5	632	14	2.26	10.24	10.53	7.27	8.27	393	20.8	14.1	5.8
112	35	16.5	Severe	Libido	f3i2/cont	0/0	0/0	f2i2/0	0	T	16	451	11.8	1.17	11.9	10.77	6.44	10.73	490	46.3	45.8	40
113	40	19.5	Profound	0	f3i2/cont	0/0	0/0	f3i1/0	0	T	17	416	13.2	1.41	12.84	13.75	7.93	12.34	285	8.3	16.7	5.2

BMI: Body Mass Index LoF: Level of Functioning IFP: Incident Free Period In Months P: Prolactin

C: Clozapine CP: Chlorpromazine ep: Sodium valproate et: Clothiapine Fl: Flupentixol H: Haloperidol O: Other

T: Thioridazine Z: Zuclopenthixol

SUMMARY OF RAW DATA: NON-AGGRESSIVE MALES

Nr.	Age	BMI	L o F	Ass symp toms	Long-term behaviour/ Observed behaviour over one month				IFP mnths	Drug	Duration mnths	P	T4	TRHST: TSH LEVELS				Cmax	DST Cortisol levels			
					Self-injury	Verbal	Property	Persons						8:00	8:20	8:40	9:30		Base line	8:00	16:00	23:00
201	56	28	Moderate	0	0/0	0/0	0/0	0/0	NA	0	0	329	11.3	4	16.35	16.87	11.62	12.87	471	14.2	8.5	2.5
202	60	23.5	Severe	0	0/0	0/0	0/0	0/0	NA	0	0	172	15.8	5.64	17.9	20.64	11.74	15	316	40	42.1	91.3
203	57	23.4	Severe	0	0/0	0/0	0/0	0/0	NA	0	0	194	16.4	1.19	7.57	9.02	5.89	7.83	337	20.3	28.5	82.5
204	54	23.6	Severe	0	0/0	0/0	0/0	0/0	NA	0	0	341	12.6	3.87	22.34	23.13	12.73	19.26	409	39.3	13.9	8.6
205	51	22	Severe	0	0/0	0/0	0/0	0/0	NA	0	0	88	16.6	1.69	12	11.98	6.76	10.31	352	37.5	12.7	3.3
206	51	18	Severe	0	0/0	0/0	0/0	0/0	NA	0	0	200	16.5	3.56	19.1	18.08	10.96	15.54	322	2905	1736	35
207	43	22.3	Severe	0	0/0	0/0	0/0	0/0	NA	0	0	176	14.9	2.06	18.74	17.14	11.6	16.68	560	24.1	14.8	8.4
208	37	18.7	Severe	0	0/0	0/0	0/0	0/0	NA	0	0	254	11.7	1.05	6.89	7.76	5.89	6.71	412	36.5	20.6	5.9
209	35	19.5	Severe	0	0/0	0/0	0/0	0/0	NA	0	0	151	13.8	1.7	10.22	10.39	6.84	8.69	474	32.9	20.9	38.6
210	31	24	Severe	0	0/0	0/0	0/0	0/0	NA	0	0	212	12.9	0.95	8.8	8.29	4.01	7.85	765	8.8	9.2	3.3
211	28	17.8	Severe	0	0/0	0/0	0/0	0/0	NA	0	0	255	12.6	0.71	5.6	6.84	4.6	6.13	463	18.9	21.9	33.1
212	27	21.5	Severe	0	0/0	0/0	0/0	0/0	NA	0	0	205	14.7	1.02	7.68	6.67	3.42	6.66	346	20	13.6	9.4
213	40	19.6	Profound	0	0/0	0/0	0/0	0/0	NA	0	0	180	12.7	1.39	5.91	8.27	6.42	6.88	516	45.1	82.7	130.7

BMI: Body Mass Index LoF: Level of Functioning IFP: Incident Free Period In Months P: Prolactin C: Clozapine

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T: Thioridazine Z: Zuclopenthixol

SUMMARY OF RAW DATA: AGGRESSIVE FEMALES

Nr.	Age	BMI	L o F	Ass. symptoms	Long-term behaviour/ Observed behaviour over one month				IFP mnths	Drug	Duration mnths	P	T4	TRHST: TSH LEVELS					DST Cortisol levels			
					Self-injury	Verbal	Property	Persons						8:00	8:20	8:40	9:30	Cmax	Base line	8:00	16:00	23:00
301	53	23	Moderate	Sleep	0/0	f2i2/0	0/0	f1i2/0	5	c+ et	24	509	14.8	1.42	12.1	11.78	6.88	10.68	414	26.9	13.2	6.9
302	48	24	Moderate	Mania	0/0	f2i2/0	f3i1/0	f2i3/ 1mild	1	C+ o	18	111	14.5	1.88	11.96	11.23	6.39	10.08	353	45.3	19.2	9.6
303	56	16.7	severe	0	f3i2/0	0/0	0/0	0/0	0	T	43	594	13.4	0.83	9.21	8.38	4.56	8.38	470	20.8	21.6	25.8
304	48	26.7	severe	0	0/0	0/0	f1i1/4mild 2 mod	f3i1/1 mild	0	H	43	944	17.4	2.62	14.41	12.2	6.36	11.79	689	41.9	25.1	14.0
305	44	25	severe	0	0/0	0/0	0/0	f1f1/0	13	T	13	1405	16.2	1.68	9.34	8.28	4.26	7.66	814	22.2	18.4	14.2
306	36	17.4	severe	0	0/0	0/0	0/0	f1i1/ 1 mild	0	H	21	111	14.4	1.2	8.4	9.1	5.41	7.9	527	58.2	33.1	308.9
307	33	27.4	severe	0	f1i1/1 mild	f1i1/2 mild	0/0	f3i2/1 mild 3 mod	0	T+z	42	1668	14.3	3.91	20.2	16.41	9.22	16.29	622	28.4	19.3	8.9
308	33	25.7	severe	0	0/0	0/0	f1i2/6 mod	0/0	0	T+ep	12	1220	13.1	1.67	18.3	18.12	9.35	16.63	602	5.3	3.5	<5.5
309	45	22	Profound	0	f3i2/continuous	0/0	0/0	0/0	0	T	156	2173	16.1	2.41	14.64	13.44	7.42	12.23	558	22.8	39.2	19.2

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SUMMARY OF RAW DATA: NON-AGGRESSIVE FEMALES

Nr.	Age	BMI	L o F	Ass sympt oms	Long-term behaviour/ Observed behaviour over one month				IFP mnths	Drug	Duration mnths	P	T4	TRHST: TSH LEVELS					DST Cortisol levels			
					Self-injury	Verbal	Property	Persons						8:00	8:20	8:40	9:30	Cmax	Baseline	8:00	16:00	23:00
401	44	25.9	Moderate	0	0/0	0/0	0/0	0/0	NA	0	0	94	15.2	1.62	14.56	11.82	5.92	12.94	321	20.5	5.9	8.6
402	43	20	moderate	0	0/0	0/0	0/0	0/0	NA	0	0	156	13.1	1.95	20.1	21.35	10.74	19.4	345	16.9	32.9	<5.5
403	54	21	Severe	0	0/0	0/0	0/0	0/0	NA	0	0	125	14.5	0.65	7.61	7.01	4.14	6.96	235	17.4	21.9	17.5
404	52	25	Severe	0	0/0	0/0	0/0	0/0	NA	0	0	203	11.6	1.74	12.69	10.21	6.65	10.95	580	17.7	30.3	129.2
405	50	28.8	Severe	0	0/0	0/0	0/0	0/0	NA	0	0	112	14.7	0.7	8.17	7.46	4.52	7.47	605	11.7	7.2	1.4
406	45	26	Severe	0	0/0	0/0	0/0	0/0	NA	0	0	148	12.8	1.7	22.87	24.2	12.31	22.5	380	13.3	10.2	12.4
407	42	22.6	Severe	0	0/0	0/0	0/0	0/0	NA	0	0	135	15.2	3.37	23.69	21.85	13.56	20.32	470	15.2	18.3	13.2
408	23	22.5	Severe	0	0/0	0/0	0/0	0/0	NA	0	0	146	13.4	0.39	6.32	6.05	2.49	5.93	252	22.6	17.4	16.3
409	50	19.5	Profound	0	0/0	0/0	0/0	0/0	NA	0	0	369	12.8	9.49	64.51	54.53	27.87	55.02	716	27.3	19.5	17.7

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