The effect of Gelsemium sempervirens 200 CH on urine cortisol levels and perceived levels of anxiety

A mini dissertation submitted to the TWR in partial fulfillment of the requirements of a Masters Degree in Technologae (Homoeopathy)

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DECLARATION

I, Karin Pelser, declare that this dissertation is my own, unaided work. It is being submitted for a Master's Degree in Technology: Homoeopathy at the Technikon Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other Technikon or University.

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Karin Pelser
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ABSTRACT

The purpose of this study was to determine whether *Gelsemium sempervirens* 200CH will have a positive effect on levels of anxiety and urinary cortisol levels in students during test conditions.

This was a double blind, placebo controlled fully randomised study and twenty first year Homoeopathy students participated in it. These students were divided into a control group and an experimental group. Each group consisted of ten participants. The students underwent the first trial about fifteen days before their test and the second trial on the day of the test. During the first trail, 24-hour urine samples were collected to determine a baseline cortisol level for each participant. They also completed an anxiety inventory (State – Trait Anxiety Inventory) to determine their levels of anxiety. The day before the test, the participants received their medication and were advised on how to take it. Each participant in the control group received three placebo powders and the participants in the experimental group received three powders containing *Gelsemium sempervirens* 200 CH. The students took one powder the afternoon before the test, the next powder the night before and the last powder the morning of the test. On the day of the test, another 24-hour urine sample was collected and the participants completed the anxiety inventory again.

The cortisol in the urine samples was determined using the Beckman Access Immunoassay System. The Access Cortisol Assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cortisol levels in human serum, plasma or urine using the Access Immunoassay System. The system software determined patients' test results automatically (Beckman Instrument Inc. 1997:1-2).

The State – Trait Anxiety Inventory (STAI) questionnaire was used to measure the students' anxiety associated with examinations (de Flores *et. al.*, 1990:706-

707). The STAI is a self evaluation questionnaire designed to measure anxiety proneness (trait) and current level of tension and apprehension (state). The inventory clearly differentiates between temporary condition of "state anxiety" and the more general and long-standing quality of "trait anxiety" (Simpson, et. al., 2001: 688-693).

The results of each subject's cortisol levels (before and during stress) and psychological tests were compared and the results of the study was analysed by a statistician by using the Wilcoxon Signed Ranks Test and the NPar Test. The results showed that the levels of state anxiety of the control group increased whereas the levels of state anxiety of the experimental groups decreased, but the difference between the two groups was not statistically significant. The levels of trait anxiety of the control group remained the same, but the anxiety levels of the experimental group decreased slightly. The levels of urinary cortisol showed a remarkable decrease in the experimental group, whereas the control group showed an increase in cortisol levels. The difference between the cortisol levels of the control and experimental group showed a statistically significant difference.

DEDICATION

To my parents, I don't know how to thank you
for your endless support during my years of study.
To Werner, thanks for your support,
understanding and help.

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CHAPTER ONE

INTRODUCTION

Most people experience some form of anxiety, which manifest as a state of physiological arousal and a generalized feeling of fear and apprehension (Bootzin, *et. al.*, 1993:590). For some, though, it is worse than for others. A typical anxiety-induced situation is illustrated in students writing a test or an exam. When a person experiences anxiety, certain physiological symptoms such as trembling, muscle tension, diarrhoea, dizziness, faintness, sweating, and heart palpitations can be identified (Weiten, 1995:567-568). Anxiety, a psychological response to stress, causes the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland, which results in the release of cortisol from the adrenal cortex causing the physiological symptoms experienced during an anxiety-induced situation (Hole, 1995:286,289).

1.1. PROBLEM STATEMENT

High levels of cortisol lead to a decrease in short-term memory and impaired attention (Vedhara, *et. al.*, 2000:535-549). This leads to poor work performance in students writing a test or exam. Chronic exposure to high levels of cortisol may lead to clinical abnormalities, such as adrenal virilism; hypersecretion of glucocorticoids producing Cushing's syndrome; and excessive aldosterone output results in aldosteronism, also referred to as Conn's syndrome (Berkow, *et. al*, 1992:1092).

1.2. HYPOTHESIS

The administration of *Gelsemium sempervirens* 200CH could significantly reduce the levels of urinary cortisol as well as the perceived levels of anxiety in students undergoing a test.

1.3. PURPOSE OF THE STUDY

The purpose of this study was to determine if *Gelsemium sempervirens* 200CH would have a positive effect on urinary cortisol levels and perceived levels of anxiety in students undergoing a test.

If *Gelsemium sempervirens* 200CH decreases urinary cortisol levels and perceived levels of anxiety, students may experience less thought interference and enhanced short term memory functioning, which may in turn, lead to improvement in test scores.

1.4. IMPORTANCE OF THE PROBLEM

A study conducted by Vedhara, et. al., (2000:535-549) showed that during an exam period the perceived levels of anxiety increased with stress, followed by a increase in the levels of cortisol. By reducing cortisol levels, short term memory and attention was enhanced. By reducing anxiety levels, it is hoped that memory, confidence and competence will improve. The marks of students may increase as their memory and competence improves and anxiety decreases.

CHAPTER TWO

REVIEW OF RELATED LITERATURE

2.1. INTRODUCTION

Anxiety is a state of physiological arousal and most people experience a generalized feeling of fear and apprehension at some stage (Bootzin *et. al.,* 1993:590). According to Weiten (1995:567) anxiety is a natural and common reaction to many of life's difficulties. The concept of anxiety usually implies a temporally ordered sequence of events that are initiated by a stressful external or internal stimulus that is interpreted as dangerous or threatening. Because intense anxiety reactions are experienced as painful or unpleasant, cognitive or behavioural operations are initiated to reduce or minimise the discomfort or pain. Anxiety is often accompanied by physiological responses such as twitching or trembling, muscle tension, headaches, sweating, irritability, fatigue, nightmares, memory problems, sexual impotence, sleeplessness, dry mouth or difficulty swallowing (http://www.medlineplus.adam.com).

2.2. ANXIETY

Anxiety states are characterised by subjective feelings of tension, apprehension, nervousness and worry due to activation or arousal of the autonomic nervous system (Spielberger, 1983:4). Sue, *et. al.,* (1994:161,162) define anxiety as feelings of fear and apprehension. Spielberger (1983:5) differentiates between state and trait anxiety. Trait anxiety refers to relatively stable individual differences in anxiety-proneness, that is, to differentiate between people in the tendency to perceive stressful situations as dangerous or threatening and to respond to such a situation with elevations in the intensity of their state anxiety reactions. Trait anxiety may also reflect individual differences in the frequency and intensity with which anxiety states have been manifested in the past, and in

the probability that state anxiety will be experienced in the future. The stronger the anxiety trait, the more probable that the individual will experience more intense elevations in state anxiety in a threatening situation (Spielberger 1983:5). Anxiety can manifest in three ways: cognitively (in the thoughts of a person), behaviourally (in the person's actions) and somatically (in the physiological or biological reactions). Cognitive manifestations can range from mild worry to panic. Behavioural manifestations of anxiety involve avoiding anxiety-provoking situations and somatic manifestations include the physical symptoms, which accompany the feeling of anxiety.

2.2.1. Symptoms of anxiety

Physiological symptoms include shallow breathing, dry mouth, cold hands and feet, elevated blood pressure, muscle tension (especially in the head, neck, shoulders and chest), indigestion (Sue *et. al.,* 1994:163), decrease in regional cerebral blood flow, trembling, diarrhoea, dizziness, faintness, sweating, and heart palpitations (Weiten, 1995:567-568). Sue *et. al.,* (1994:162) states that high levels of anxiety and fear can lead to psychomotor and intellectual errors. It can also impair psychological functioning and disturb concentration and memory. Mild or moderate anxiety however, may serve a useful or adaptive function. It is believed that moderate anticipatory anxiety about realistic threats is necessary for the development of coping behaviour.

2.2.2. Behavioural responses to anxiety

Mason (1968:576-607) emphasised the importance of psychological variables in adrenocortical stress responses. He considered the following as important: the quality of emotional reactions, the effectiveness of psychological defences, and the acute or chronic nature of the threat. Several studies investigating these factors reported effects of coping on the hypothalamic-pituitary-adrenal (HPA) axis response to stress (Houtman and Bakker, 1991:11-24; Ursin and Olff,

1993:66-71). According to Henry (1992:66-83) coping is related to lower adrenocortical responses to stress, while unsuccessful coping is associated with helplessness or hopelessness, which leads to higher adrenocortical activity. The use of denial and other defence mechanisms in stressful situations has also been found to be associated with increased adrenocortical activity (Ursin and Olff, 1993:71).

According to Weiten (1995:526-527) most behavioural responses to anxiety involves coping. People cope with anxiety in many ways, but most individuals exhibit certain styles of coping that are fairly consistent across situations (Endler and Parker, 1990:1040-1048). Some of these coping strategies involve striking out at others with aggressive behaviour, giving up and withdrawing from the battle. Anxiety sometimes leads to self-indulgence. When troubled by anxiety, many people engage in excessive consummatory behaviour for example, eating, drinking, smoking, using drugs, and so forth. Many people exhibit styles of defensive coping in response to anxiety. Many specific defence mechanisms have been identified. Common defence mechanisms include denial of reality, fantasy, intellectualisation, undoing, and overcompensation (Weiten, 1995:529). If the person is unable to cope with, or reduce the stress, he or she may resort to intrapsychic manoeuvres (psychological defences) that serve to eliminate the anxiety state or to reduce its level of intensity (Wolman, 1996:44). Baker and Fabian (2001:30) identified the following behavioural manifestations: social withdrawal, disturbed sleep, increased aggression and irritation, loss of sexual interest, and increased obsessional tendencies.

A study conducted by Pruessner, *et. al.,* (1997:616-622) suggested that there is an association between psychological variables and cortisol responses after repeated exposure to psychosocial stress. This association is best explained by the HPA axis, which is activated in response to internal or external stimuli, and which leads to the release of cortisol. A study by Malarkey, *et. al.,* (1995:499-508) on students during examinations, suggested that the levels of cortisol

increased significantly from the baseline levels when the students experienced the most stress. The nature of the stressor and the state of the responder were of equal importance in the observed cortisol response during examination.

Several studies tried to uncover possible associations between cortisol stress responses and personality variables. Variables investigated include, trait anxiety (Hubert and de Jong-Meyer: 1992:115-120), extraversion and neuroticism (Arnetz and Fjellner, 1986:297-305), sensation seeking (Kirschbaum, *et. al.,* 1992:1353-1357), achievement motivation (Lehmann, *et. al.,* 1992:1-8), or locus of control (Seeman, *et. al.,* 1995:69-84). However, the relationship between HPA axis stress responses and personality traits is less consistent, and many studies failed to show effects of personality traits on HPA axis stress responses (Blood, *et. al.,* 1994:760-768; van Eck, *et. al.,* 1996:432-446). One reason for this inconsistency is the fact that the cortisol stress response reflects a state measure, which depends only in part on the personality of the subject, but also on the acquired coping strategies, the probability of success in the given situation, and the relationship between them. Thus, in order to reveal consistent associations between personality traits and cortisol stress responses, the trait component of the cortisol stress response needs to be determined (Prussner, *et. al.,* 1997:616).

A study conducted by Vedhara, *et. al.,* (2000:535-549)) showed that during an exam period the perceived levels of anxiety increased with stress, followed by a increase in the levels of cortisol. By reducing cortisol levels, short term memory and attention was enhanced.

2.2.3. Measurement of anxiety

In a study conducted by de Flores, *et. al.,* (1990:706-707), the State–Trait Anxiety Inventory (STAI) questionnaire was used to measure the students' anxiety associated with the examinations. The study showed different levels of

anxiety in examinations of different subject matters, with a positive correlation between the importance attributed to the examination and the associated anxiety.

According to Spielberger (1999:1), there are numerous test instruments for quantifying a patient's degree of anxiety. Self-rated anxiety scales include the Beck Anxiety Scale, IPAT Anxiety Scale and the STAI. These are filled out by the patient, and so understandably reflect the patient's subjective feelings (assuming, of course, the patient fills out the form honestly and is in touch with his or her feelings). Other instruments, such as the Hamilton Anxiety Scale, are observer-related. This means that a presumably objective clinician completes the ratings for various items. The Hamilton scale, for example, consists of 14 items examining 89 possible symptoms of anxiety, with each item rated on five levels of severity. In the sense that an outside observer does the rating, one could say that this is an objective test instrument. But it still depends on the patient's co-operation and honesty. Because anxiety is an internal, psychic state, it is difficult to get an objective measure of its degree.

Cattell (1966; Cattell and Scheier, 1961, 1963) was first to introduce the concept of state and trait anxiety and Spielberger (1966, 1972, 1976, 1979) elaborated on this. An emotional state exists at a given moment in time and at a particular level of intensity. The STAI is a self-evaluation designed to measure anxiety proneness (trait) and current level of tension and apprehension (state). This test clearly differentiates between temporary condition of "state anxiety" and the more general and long-standing quality of "trait anxiety" (Simpson, *et. al.,* 2001:688-693).

The STAI state anxiety scale evaluates feelings of apprehension, tension, nervousness, and worry. Scores on the state anxiety scale increases in response to physical danger or psychological stress and decreases as a result of relaxation training. The scale has been used extensively to assess the level of state anxiety

induced by stressful events such as writing a test (Simpson, *et. al.*, 2001:688-693).

2.3. CORTISOL

Cortisol is one of the main glucocorticoid hormones in the body. It is produced and secreted from the adrenal cortex and has multiple metabolic functions (Guyton and Hall, 1996:926).

2.3.1. Secretion of Cortisol

Hole (1995:286) states that the release of cortisol is controlled by a negative feedback mechanism, which involves three major organs. These include the hypothalamus, the anterior pituitary gland, and the adrenal cortex. The hypothalamus secretes corticotropin–releasing hormone (CRH) into the hypophyseal portal veins. These blood vessels carry CRH to the anterior pituitary gland, which stimulates the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH). ACTH in turn causes the adrenal cortex to secrete cortisol. In the CRH–ACTH–cortisol sequence, the final hormone (cortisol) acts upon the hypothalamus to reduce the secretion of CRH by causing a decrease in the frequency of action potentials in the neurons secreting CRH. In addition, cortisol acts directly on the anterior pituitary gland to reduce the response of the ACTH–secreting cells to CRH. Thus, by a double–barrelled action, cortisol exerts a negative–feedback control over its own secretion (Vander, *et. al.*, 1994:292).

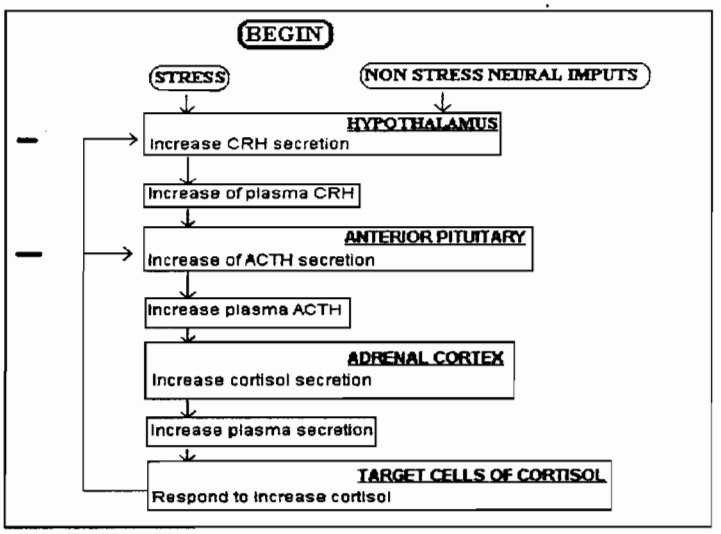


Figure 2. 1. The CRH–ACTH-Cortisol sequence (Vander *et. al.*, 1994:294)

2.3.2. Actions of the hormone, cortisol

Hole (1995:286) highlights three main actions of cortisol. These include:

- Inhibition of the synthesis of protein in various tissues, thus causing an increase in the blood concentration of amino acids.
- Promotion of the release of fatty acids from adipose tissue, thus causing an increase in the use of fatty acids as an energy source and a decrease in the use of glucose for this purpose.
- Stimulation of the liver cells to form glucose from non-carbohydrates, such as circulating amino acids and glycerol, thus promoting an increase in the blood glucose concentration.

These actions help to keep the concentration of blood glucose within normal range between meals, because the supply of glycogen stored within the liver can be exhausted in a few hours without food.

2.3.3. Effect of physiological and psychological stress on secretion of cortisol

Hole (1995:286) states that survival depends on the maintenance of homeostasis. Certain factors might cause changes in the body's internal environment which may be life threatening. Nerve impulses are directed to the hypothalamus when dangers are sensed. Physiological responses are triggered that tend to maintain homeostasis. These responses include increased activity in the sympathetic division of the autonomic nervous system and an increase in the secretion of adrenal and other hormones. Responses to stressful events are generally regarded as reactions of the organism to accommodate to or compensate for stress. This reaction is classically described as an activation of the sympathoadrenal system and the HPA axis, resulting in increases in plasma level of norepinephrine, epinephrine, ACTH and cortisol (Bernards, *et. al.,* 2000:866-872). These factors are referred to as stressors, and the condition it produces in the body is called a stress. Physical stressors include exposure to extreme heat or cold, decreased oxygen concentration, infections, injuries, prolonged heavy exercise, and loud sounds. Stressors can also be psychological factors such as thoughts about real or imagined dangers, personal losses, and unpleasant social interactions. Psychological stress can result from feelings of anger, fear, grief, anxiety, depression or guilt (Hole 1995:288-289).

According to Skosnik, *et. al.,* (2000:59-68) two of the most important responses to stress are increased norepinephrine and cortisol activities. These physiological responses are directed towards maintaining homeostasis, and they usually involve a set of reactions called the general stress syndrome, which is largely controlled by the hypothalamus.

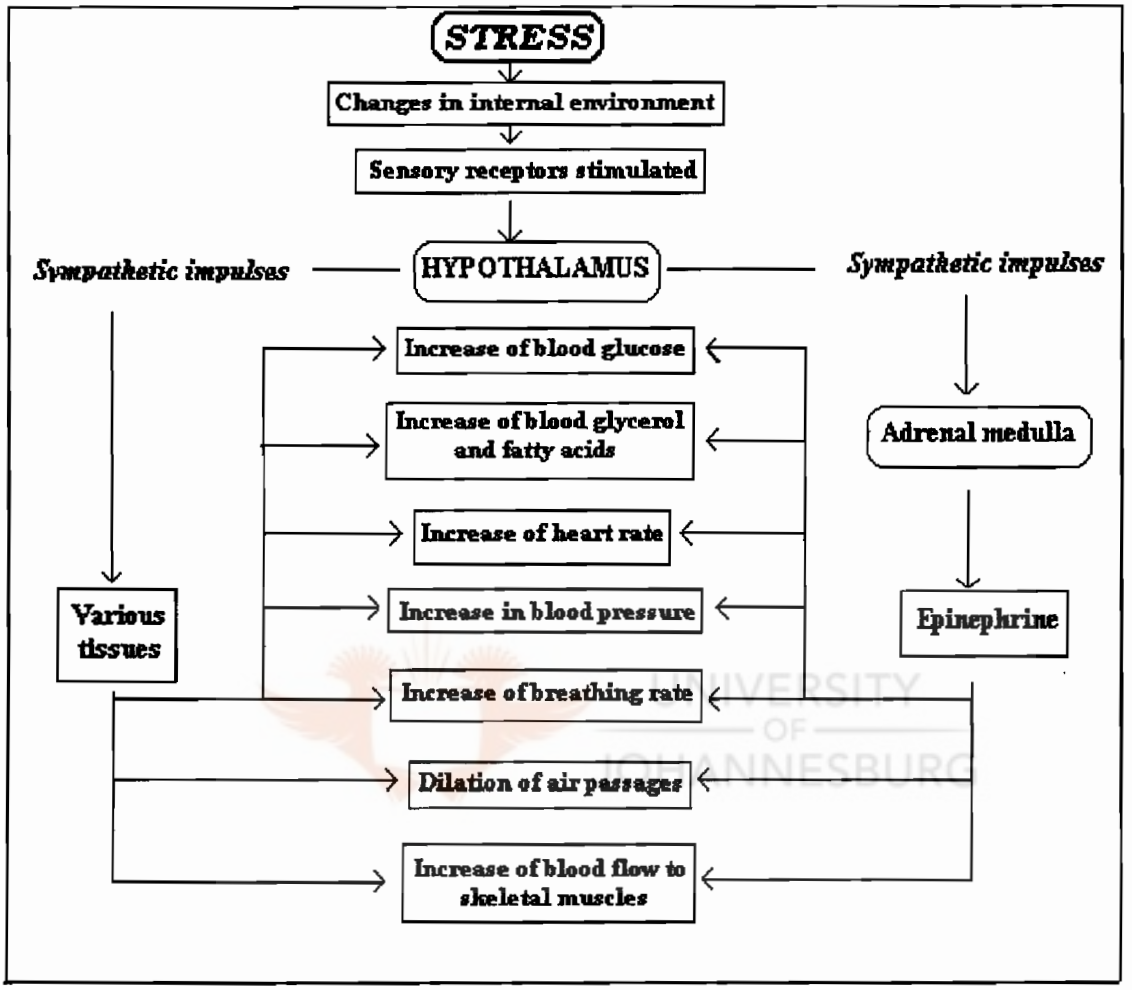


Figure 2.2. The sympathetic impulses triggered by the hypothalamus during times of stress (Hole, 1995:288)

Typically the hypothalamus responds to stress by the activation of the "fight or flight" response. During this response the hypothalamus activates the adrenal medulla to release epinephrine, which causes a rise in the blood glucose concentration, increase in heart rate, rise in blood pressure, an increase in breathing rate, dilation of the air passages, a shunting of blood from the skin and digestive organs into the skeletal muscles (Hole, 1995:288-289).

At the same time the hypothalamus releases CRH, which in turn leads to the release of ACTH and finally the release of cortisol. Cortisol promotes an increase in blood amino acid concentration, the release of fatty acids, and the formation of

glucose from non-carbohydrates. Thus, while the body is preparing itself for physical activity, the actions of cortisol supply the cells with substances that may be needed during times of stress (Hole, 1995:288-289).

Stress also leads to an increase in secretion of other hormones, like glucagon, growth hormone, and antidiuretic hormone (Hole, 1995:288-289).

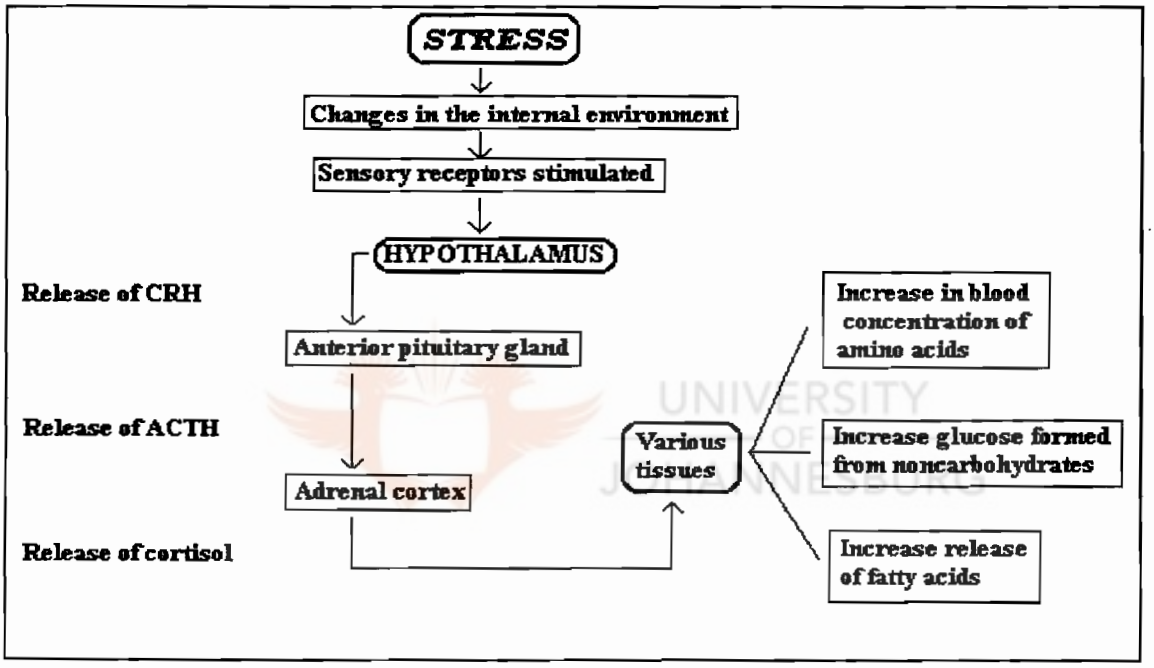


Figure 2.3. The release of cortisol by the adrenal cortex to resist the effects of stress (Hole, 1995:288)

2.3.4. Fluctuation of cortisol levels

The normal reference value of cortisol in 24-h urine sample is 9 – 50 μmol/mol creatine (Boon, *et. al.,* (1999:1136). Marlarkey, *et. al.,* (1995:499-508) stated that the mean concentration of urinary cortisol levels increased significantly in relation to the perceived levels of anxiety, but that the examination stress did not significantly affect day or night mean cortisol levels from baseline to examination week. Cortisol is the final product of the pathway leading to the synthesis of glucocorticoids in the adrenal cortex (Nomura, *et. al.,* 1997:83). Recent studies

conducted by Schmidt-Reinwald, *et. al.,* (1999:1653-1654) showed that cortisol levels rapidly increase within the first thirty minutes after awaking. This is because of the activity of the HPA axis that is characterised by a circadian rhythm with the highest spontaneous secretory activity during the second half of nocturnal sleep with decreasing activity thereafter. This pattern is associated with peak levels of ACTH and cortisol in the early morning hours followed by a continuous decline during the day. It is documented that within the first thirty minutes after awakening the free cortisol levels rise by 50-150% and remain elevated for at least sixty minutes.

2.3.5. The anatomy and physiology of the organs which play a role in the secretion and control of cortisol

The hypothalamus

The hypothalamus forms the floor and part of the lateral walls of the third ventricle of the brain and lies inferior to the thalamus. Many nuclei are located in the hypothalamus output (Solomon, *et. al.,* 1990:450-451). Nerve fibres to the cerebral cortex, thalamus, and other parts of the brain stem interconnect the hypothalamus so that it can receive impulses from them and send impulses to them (Hole, 1995:225). The hypothalamus is a small but mighty part of the brain, and helps to regulate an impressive number of mechanisms essential to maintaining homeostasis.

The pituitary gland (hypothysis)

The pituitary gland is located at the base of the brain, where it is attached to the hypothalamus by the pituitary stalk (infundibulum). The gland is about 1 cm in diameter and consists of two distinct portions or lobes, the anterior lobe and the posterior lobe. The brain controls most of the pituitary gland's activities. The release of hormones from the posterior lobe occurs when nerve impulses from

the hypothalamus signal the axon ends of neurosecretory cells in the posterior lobe. Releasing hormones produced by the hypothalamus controls secretions from the anterior lobe (Hole, 1995:278).

The anterior pituitary hormones: The anterior lobe of the pituitary gland is enclosed by a capsule of dense collagenous connective tissue and consists largely of epithelial tissue arranged in blocks around many thin–walled blood vessels. The following are hormones released by the anterior pituitary gland: Growth hormone (GH), prolactin (PRL), thyroid–stimulating hormone (TSH), and adrenocorticotropic hormone (ACTH). The fifth type of cell secretes follicle–stimulating hormone (FSH) and luteinizing hormone (LH). In males, luteinizing hormone is known as interstitial cell stimulating hormone or ICSH (Hole, 1995:278).

The Anterior pituitary gland and the Hypothalamus: The hormones released from the hypothalamus to the pituitary gland are collectively termed hypophysiotropic hormones or are commonly known as hypothalamic releasing hormones. The hypophysiotropic hormones denote only those hormones from the hypothalamus that influence the anterior pituitary gland. Each of the hypophysiotropic hormones is the beginning of a sequence of three hormones: (1) A hypophysiotropic hormone controls the secretion of (2) an anterior pituitary hormone, which controls the secretion of (3) a hormone from some other endocrine gland. This last hormone then acts on its target cells (Vander, *et. al.,* 1994:287-288).

The Adrenal glands

The adrenal glands are closely associated with the kidneys. A gland sits on top of each kidney, like a cap and is embedded in the mass of fat that encloses the kidneys. Each adrenal gland is very vascular and consists of two parts: the central portion or adrenal medulla and the outer portion or the adrenal cortex.

These regions are not sharply divided; they represent distinct glands that secrete different hormones (Hole, 1995: 284-285).

The adrenal medulla consists of irregularly shaped cells that are arranged in groups around blood vessels. These cells are intimately connected with the sympathetic division of the autonomic nervous system. The adrenal medulla cells are modified postganglionic neurons, and preganglionic autonomic nerve fibres lead to them from the central nervous system. The cells of the adrenal medulla secrete two closely related hormones, epinephrine (adrenaline) and norepinephrine (noradrenaline). These hormones have similar molecular structure and influence the same organs, but have opposing physiological functions (Hole, 1995: 284-285).

The adrenal cortex makes up the bulk of the gland, and is composed of closely packed masses of epithelial cells, which are arranged in layers. These layers form an outer, middle and inner zone of the cortex. These cells are also well vascularised. The cells of the adrenal cortex produce over thirty different steroids, among which are several hormones. The most important adrenal cortical hormones are aldosterone, cortisol and sex hormones (Hole, 1995: 284-285).

2.3.6. Abnormalities related to cortisol

The hyposecretion of cortical hormones, aldosterone and cortisol leads to a condition called Addison's disease or Hypoadrenalism (Solomon, *et. al.,* 1990:632). This condition is characterised by a decrease in blood sodium, increased blood potassium, low blood glucose concentration (hypoglycaemia), dehydration, low blood pressure, and increased skin pigmentation (Hole, 1995:286). Reduction in cortisol secretion prevents the body from regulating blood glucose levels because it cannot synthesise enough glucose through gluconeogenesis. The patient loses the ability to cope with stress; if cortisol

levels are significantly depressed, even the stress of mild infections can cause death (Solomon, *et. al.,* 1990:632).

Hypersecretion of cortical hormones result in a condition called Cushing's syndrome or Hyperadrenalism (Solomon, *et. al.,* 1990:632). This may be associated with an adrenal tumour or with an oversecretion of ACTH by the anterior pituitary gland. A person with this condition has changes in carbohydrate and protein metabolism and in electrolyte balance. The effect on protein catabolism is profound, and causes a decrease in tissue proteins almost everywhere in the body except the liver and plasma proteins. The loss of protein from the muscles in particular causes severe weakness. The loss of protein synthesis in the lymphoid tissue leads to a suppressed immune system, so that many of these patients die from infection. Even the protein collagen fibres in the subcutaneous tissues tear easily, resulting in the development of large purplish striae where the subcutaneous tissues have torn apart. In addition, severely diminished protein deposition in the bones often causes severe osteoporosis with consequent weakness of the bones (Guyton and Hall, 1996:968). The abundance of cortisol secreted can cause increased concentrations of blood glucose, abnormal retention of sodium, and as a result the tissue fluids tend to increase, and the skin becomes puffy. At the same time, an increase in the adrenal sex hormones may produce masculinising effect in the female, such as the growth of a beard or development of a deeper voice (Hole, 1995:287).

2.4 TREATMENT FOR ANXIETY

Anxiety disorders are treated with some form of counselling or psychotherapy or pharmacotherapy, either singly or in combination (Barlow and Lehman, 1996:727-735; American Psychiatric Association, 1998:1; Kent, *et. al.,* 1998:812-824).

There are also non-benzodiazepine anxiolytics. These include:

- **Antihistamines:** These drugs are sedating rather than being true anxiolytics and may result in a sedated but internally agitated patient. They also have considerable potential for inducing delirium owing to their anticholinergic effect. Because of this, these agents are considerably less desirable for the treatment of anxiety (Berkow, *et. al.*, 1992:1634). .
- **Antipsychotics:** These exert an anti-anxiety effect, but risk for dyskinesia and neuroleptic malignant syndrome precludes their use for this indication (Berkow, *et. al.*, 1992:1634). .
- **Barbiturates:** Prior to the advent of benzodiazepines, these were the agents of choice for the treatment of anxiety. These are sedatives that have a calming effect, but are highly addictive (Sue *et. al.* 1994:541). Because of their toxicity, they have been superseded by the benzodiazepines for this indication. They are far more lethal in overdose, withdrawal syndromes are more common and more dangerous, and their abuse liability is much higher (Berkow, *et. al.*, 1992:1634).
- **β - Blockers:** β-Blockers do a very reasonable job treating the peripheral manifestations of anxiety. β-Blockers do very little to affect the cognitive parts of anxiety, so that while the tremor, the tachypnea, and the palpitations improve, the sense of dread is not altered for most. β-Blockers are most clearly effective for those suffering from performance anxiety (Berkow, *et. al.*, 1992:1634).
- **Buspirone:** These drugs have limited toxicity. It does not cause sedation, interact with alcohol, affect the seizure threshold, nor is it a muscle relaxant. Its abuse liability is very low. Since it does not interact with the benzodiazepine receptor, it cannot be directly substituted for a benzodiazepine that has been in long-term use as the patient may experience benzodiazepine withdrawal (Berkow, *et. al.*, 1992:1634).

Antidepressants:

Most antidepressant medications have substantial antianxiety and antipanic effects in addition to their antidepressant action (Kent, *et. al,* 1998:812-824). Moreover, a large number of antidepressants have antiobsessional effects. In observation that the tricyclic antidepressant imipramine had a different anxiolytic profile than diazepam, helped to differentiate panic disorder from generalised anxiety disorder and, subsequently, social phobia (Perry, *et. al.* 1997:472-477). .

When effective in treating anxiety, antidepressants should be maintained for at least 4 to 6 months, then tapered slowly to avoid discontinuation-emergent activation of anxiety symptoms (March, *et. al.,* 1997:2-72). Although less extensively researched than depression, it is likely that many patients with anxiety disorders may warrant long term, indefinite treatment to prevent relapse or chronicity (Ballenger, *et. al*, 1998:54-60).

2.4.2. Psychotherapy

According to Sue *et. al.,* (1994:545-546), drug therapy is used as an adjunct to psychotherapy. Psychotherapy may be defined as the systematic application of techniques derived from psychological principles by a trained and experienced professional therapist. Therapists seek to modify attitudes, thoughts and feelings (American Psychiatric Association, 1998:1-34).

Counselling and Psychotherapy:

Anxiety disorders are responsive to counselling and to a wide variety of psychotherapies. More severe and persistent symptoms may also require pharmacotherapy (American Psychiatric Association, 1998:1-34).

There has been increasing enthusiasm for more focused, time-limited therapies that address ways of coping with anxiety symptoms more directly rather than

exploring unconscious conflicts or other personal vulnerabilities. These therapies typically emphasise cognitive and behavioural assessment and interventions (Barlow and Lehman, 1996:727-735).

The hallmarks of cognitive-behavioural therapies are evaluating apparent cause and effect relationships between thoughts, feelings and behaviours, as well as implementing relatively straightforward strategies to lessen symptoms and reduce avoidant behaviour (Barlow, 1988). A critical element of therapy is to increase exposure to stimuli or situations that provoke anxiety. Without such therapeutic assistance, the sufferer typically withdraws from anxiety-inducing situations, inadvertently reinforcing avoidant or escape behaviour (Shear, 1995:885-894).

It is possible that more traditional forms of therapy based on psychodynamic or interpersonal theories of anxiety also may prove to be effective treatments (Shear, 1995:885-894).

Combination of Psychotherapy and Pharmacotherapy:

Some patients with anxiety disorders may benefit from both psychotherapy and pharmacotherapy treatment modalities, either combined or used in sequence (March, *et. al.* 1997:2-72; American Psychiatric Association, 1998:1-34). Drawing from the experiences of depression researchers, it seems likely that such combinations are not uniformly necessary and are probably more cost-effective when reserved for patients with more complex, complicated, severe or comorbid disorders. The benefits of multimodal therapies for anxiety need further study (March, *et. al.* 1997:2-72).

2.4.3. Homoeopathic treatment

Within the total concept of medicine, homeopathy may be defined as a form of regulatory therapy. The aim is to influence autoregulation with the aid of a remedy, which relates to the way the individual patient, reacts (Koehler, 198618). Boyd (1982:2,3) describes homoeopathy as a system of therapeutics for treating people and animals on the basis of the simile principle. The word "homoeopathy" is derived from the Greek words *homoios* meaning "like or similar" and *pathos* meaning "suffering". This forms the basis of homoeopathy. The most successful remedy for any given occasion will be that one whose symptomatology presents the clearest and closest resemblance to the symptom–complex of the sick person in question, i.e. "Similia similibus curentur", meaning "Let likes be treated by likes" (Boyd, 1982:2,3).

2.4.3.1. General principles of Homoeopathic treatment

According to Eizayaga (1991:35) Homoeopathy is a science and an art of preventing and treating disease. It is a therapeutic approach based on certain principles or rules. These principles include:

The Law of Similars: The law of similars matches the symptom manifested in the patient with the analogous symptom of a therapeutic substance manifested in a healthy individual to establish resonance between patient and remedy. The law of similars states that any substance, which can produce a totality of symptoms in a healthy human being, can cure that totality of symptoms in a sick person (Vithoulkas, 1980:98).

Provings on healthy person: According to Eizayaga (1991:36) the detailed relations of all symptoms provoked by a medicament in a healthy individual is called a proving or pathogenesis. During a proving, a substance sufficiently high in concentration, is introduced into an individual. This substance disturbs the individual and mobilises its defence mechanism. The defence mechanism

produces a spectrum of symptoms on all three levels of the individual; this spectrum of symptoms then characterises the peculiar and unique nature of the substance. All these symptoms from the patient are then recorded (Vithoulkas, 1980:97).

Diluted, attenuated and dynamised medicine: Hahnemann (Eizayaga, 1991:37) demonstrated that the more dilute and dynamised (by the process of succussion) a remedy is, the more efficacious and penetrating in its action it will be and that the quantity of the drug required is inversely proportional to its similarity with the symptoms of the patient (Eizayaga, 1991:37).

The single remedy: According to Eizayaga (1991:37), there is usually only one medicine that covers the actual state of the patient and only that most similar remedy should be given. When the symptoms change, it will be necessary to give the patient the new similar remedy according to the new morbid state.

2.4.3.2. Gelsemium sempervirens for the treatment of anxiety

According to Sankaran (1997:85), a patient who needs *Gelsemium sempervirens* suffers from ailments of anticipation. The person gets apprehensive in the face of ordeals and develops a lack of confidence in such a situation. Tyler (1996:382) refers to *Gelsemium sempervirens* as the "great paralyser." The mental prostration is typified in anxiety, as before an examination, and is accompanied by drooping eyelids, hysterical dysphagia or aphonia, followed by tremors. There is also diarrhoea from anticipation. Beside the anticipation, *Gelsemium sempervirens* is also indicated for exam anxiety.

Vermeulen (1997:770-771) lists the following symptoms pertaining to a patient who needs *Gelsemium sempervirens:* stage fright, lethargy, and dullness of mind with incapacity to think or fix attention. The patient complains of trembling from exhaustion or fear, even his voice trembles. He has an aversion to mental work and vanishing of thoughts. There are physical complaints of nervous exhaustion

or emotional excitement including diarrhoea and urinary frequency, loss of voice, difficulty breathing, stomach cramps, and headaches. When he is anxious it feels as if his heart will stop beating. Furthermore, he may also experience anticipatory anxiety before an exam, cowardice, lack of confidence and loss of memory.

When faced with a stressful situation, the *Gelsemium sempervirens* state is characterised by apprehension, loss of memory, stupor, weakness of mind and body. He is slow, sluggish, dull, almost paralysed. Trembling is a marked feature. There is a tendency towards nervous diarrhoea (Sankaran, 1994:270-271).

Choice of potency

According to Vithoulkas (1980:213-217) there are no set rules regarding the selection of the potency, only guidelines. A study conducted by Traub (2000:33-35), on university students during examination conditions showed that by using a complex remedy containing *Kalium phosphoricum* 200CH, *Argentum nitricum* 200CH and *Gelsemium sempervirens* 200CH, feelings of anxiety decreased by 15,42 % and thought interference decreased by 11,88 %. In this study *Gelsemium sempervirens* 200CH will be used alone, in an attempt to study the effect of this single remedy on levels of anxiety and urine cortisol levels in students undergoing a test. *Gelsemium sempervirens* 200CH was chosen to see if it was the *Gelsemium sempervirens* 200CH that was responsible for the changes in thought interference and feelings of anxiety.

CHAPTER THREE

METHODOLOGY

3.1. DURATION AND TYPE OF THE STUDY

The research study was conducted over fifteen days. It was started fifteen days before the students wrote a test and ended when the students had written their test. This was a double blind, placebo controlled fully randomised study.

3.2. SAMPLE SIZE

Thirty students were recruited for the study, but only twenty students completed the study. Of these, ten were allocated to the experimental group, which received medicated *Gelsemium sempervirens* powders. Ten students were allocated to the control group, which received placebo powders.

3.3. SELECTION OF RESEARCH SUBJECTS

Subjects were selected on a voluntary basis. The selected participants completed the consent forms (Appendix A). They were divided into two groups; an experimental group (ten students) and a placebo-control group (ten students). An independent person randomised the sample. Owing to the double-blind nature of the study, neither the researcher nor the subjects were aware of the composition of the medication.

3.4. SUBJECT SCREENING

The subjects were considered eligible for the study if the following criteria were met:

- Subjects had to be tertiary students between the ages of 18 and 30 years;

- They should not have had any underlying illnesses e.g. attention deficit disorder, epilepsy or any other systemic disorders that may influence the results;
- Should not have taken any medication for nervousness or anxiety. The subjects were selected from people who have been exposed to the same environmental conditions, (i.e. writing the same test on the same day, in the same venue).

3.5. INVESTIGATING PROCEDURES

Fifteen days before the test, a 24-hr urine sample of each of the students was collected to determine a baseline cortisol level. Each student was issued a two-litre bottle for the collection of urine, which was returned the next day. The bottles were stored at the clinic laboratory for use at their discretion. They were advised how to collect the urine sample by means of a pamphlet (Appendix B). A laboratory, Autopath analysed the urine samples and determined the baseline cortisol levels. Each student also underwent a psychometric test, called the State–Trait Anxiety Inventory (STAI), which took ten minutes. A registered psychologist administered, scored, and interpreted the anxiety inventory. Each student received his/her medication. They were advised how to take the medication by means of a pamphlet (Appendix C). The students in the experimental group each received three medicated powders *Gelsemium sempervirens* 200CH and the students in the placebo-control group each received three placebo powders (i.e. lactose powders). The medication was taken the morning before the test, the night before the test and the morning of the test.

The day before the test, the students received another two-litre bottle to collect a 24-hour urine sample. Half an hour before the test the next day, the students underwent the same psychometric test, which took ten minutes. A registered psychologist administered, scored, and interpreted the anxiety inventory. Bottles

were available for the students during the test. At the end of the day, all the bottles were collected and Autopath analysed the levels of cortisol during the period of anxiety.

3.6. MEASURING TOOLS

3.6.1. The State-Trait Anxiety Inventory

Description and application of the State–Trait Anxiety Inventory (STAI): The STAI has been used extensively in research and in clinical practice. It comprises separate self-report scales for measuring state and trait anxiety. The state anxiety scale (STAI Form Y-1) consists of twenty statements that evaluate how respondents feel "right now, at this moment". The trait anxiety scale (STAI Form Y-2) consists of twenty statements that assess how people generally feel. The STAI-Y state anxiety and trait anxiety scales are printed on opposite sides of a single-page test form (Spielberger 1983:6-7).

The STAI trait anxiety scale has been widely used in assessing clinical anxiety and has proven useful for identifying persons with high levels of neurotic anxiety (Spielberger 1983:6-7).

Administration of the STAI: It was designed to be self-administering and may be given either individually or to groups. The inventory has no time limits. College students generally require about six minutes to complete either the state anxiety or the trait anxiety scale, and approximately ten minutes to complete both (Spielberger 1983:9).

Scoring: Each STAI item is given a weighted score of 1 to 4. A rating of 4 indicates the presence of high levels of anxiety (Spielberger 1983:12).

Reliability: The stability, as measured by test-retest coefficients, is relatively high for the STAI trait anxiety scale and low for the state anxiety scale, as would be expected for a measuring tool assessing changes in anxiety resulting from situational stress. The internal consistency for both the state anxiety scale and the trait anxiety scale are quite high as measured by alpha coefficients and item-remainder correlations. The overall median alpha coefficient for state anxiety and trait anxiety scales for the Y-Form in normative samples are 0.92 and 0.90 respectively (Spielberger 1983:32).

3.6.2. Assessment of cortisol: Beckman Access Immunoassay System

The Access Cortisol assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cortisol levels in human serum, plasma (heparin, EDTA) or urine using the Access Immunoassay System (Beckman Instrument Inc. 1997:1-2).

Principles and procedures of the test:

The Access Cortisol assay is a competitive binding immunoenzymatic assay. A sample is added to a reaction vessel with rabbit antibody to cortisol, cortical-alkaline phosphatase conjugate, and paramagnetic particles coated with goat anti-rabbit capture antibody (Beckman Instruments, Inc. 1997). After unbound particles are removed by washing, a chemiluminescent substrate, Lumi-Phos 530, is added to produce light directly proportional to the amount of analyte in the sample as determined from a stored calibration curve (Laffin, *et. al.,* 2001:129).

Specimen collection and preparation:

A 24-hour urine specimen is collected into a container with 10 gm of boric acid added as a preservative. The total volume of urine is recorded (Beckman Instruments, Inc. 1997).

Results:

The system software determines patients' test results automatically. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration curve (Beckman Instruments, Inc. 1997).

3.7. DATA CAPTURE AND STATISTICAL ANALYSIS

The results of each subject's cortisol levels (before and during stress) and psychological tests were compared and the results of the study was analysed by a statistician by using the Wilcoxon Signed Ranks Test and the NPar Test. The results were documented. In the following chapter these results will be given, with an interpretation thereof in the subsequent chapter.

CHAPTER FOUR

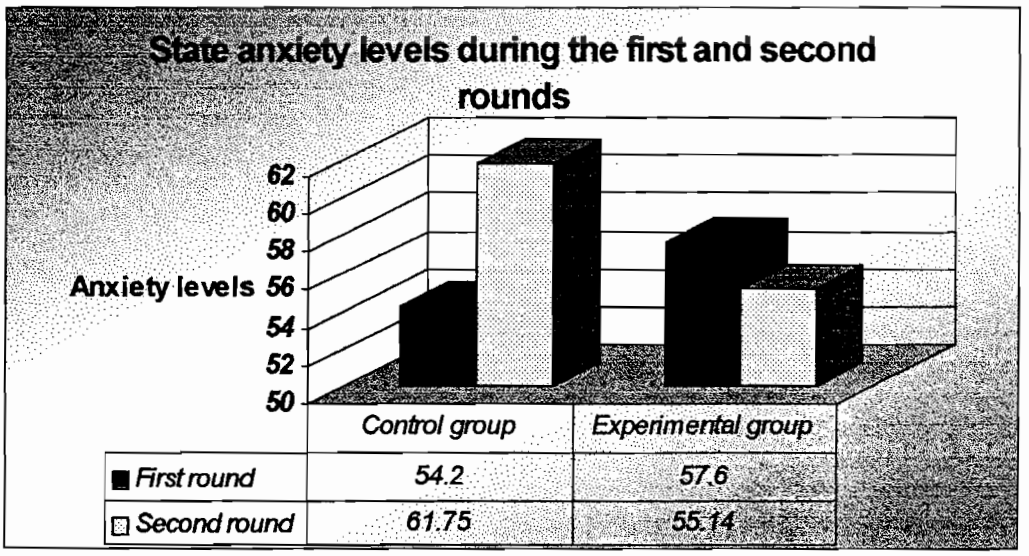
RESEARCH RESULTS

[1]4.1. INTRODUCTION

Thirty students from the Technikon Witwatersrand were involved in this study. Due to dropouts, only twenty students completed the study. All twenty students were compliant, thus none of the results were excluded.

4.2. ANXIETY LEVELS

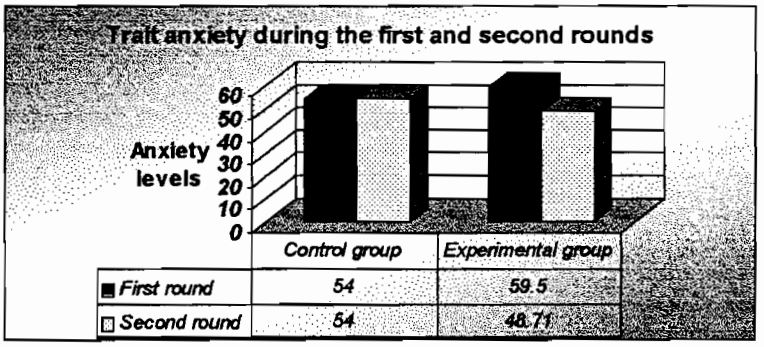
The experimental group showed a slight decrease in state anxiety levels, whereas the control group showed an increase in levels of anxiety (Refer to Graph 4.2.1).



Graph 4.2.1 Graph illustrating the difference in the levels of state anxiety

[1] See Appendix D for raw data

The trait anxiety of the control group remained unchanged, but the experimental group showed a slight decrease in trait anxiety (Refer to Graph 4.2.2).

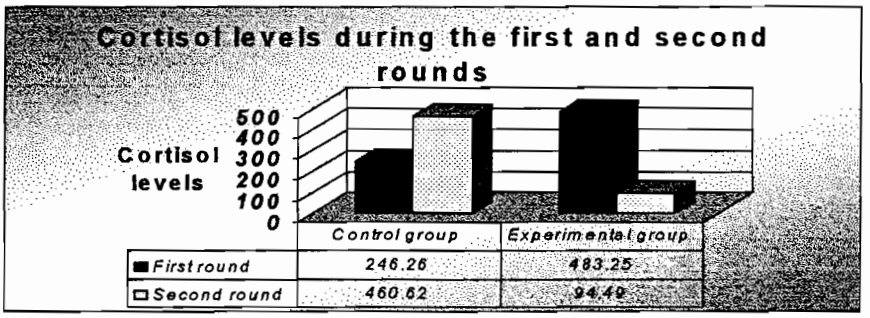


Graph 4.2.2. Graph illustrating the difference in levels of trait anxiety

When the decrease was analyzed by comparing the levels of anxiety during the first and second round, there was no significant statistical decrease, because the P-Values of the state anxiety of both groups was less than 0.005. The P-Value of the state anxiety of the control group was 0.35 and that of the experimental group 0.23. The P-Values for the trait anxiety of the experimental group was 0.08 and that of the control group 0.06.

4.3. CORTISOL LEVELS

When comparing the cortisol levels of the control and experimental groups, the control group showed an increase in cortisol levels during the second round, whereas the experimental group showed a significant decrease in cortisol levels, (Refer to Graph 4.3.1).



Graph 4.3.1. Graph illustrates the difference in cortisol levels

When the difference in cortisol levels were analyzed, it showed a statistical significant difference because the P-Values of the experimental group was less than 0.005. The P-Value of the control group was 0.385 and that of the experimental group 0.0058.

4.4. SUMMARY

	State anxiety		**Cortisol levels**	
	Control group	*Experimental group*	*Control group*	*Experimental group*
First round	54.2	57.6	246.26	483.25
Second round	61.75	55.14	460.62	94.49

Table 4.4.1. Table illustrating the correspondence between the levels of state anxiety and the cortisol levels

The table above shows the correspondence between the mean values of state anxiety levels and urinary cortisol levels. The control group shows an increase in both state anxiety and cortisol levels during the second round. Whereas the experimental group shows a slight decrease in state anxiety, but the cortisol levels decreased remarkably.

CHAPTER FIVE

DISCUSSION OF RESEARCH RESULTS

5.1. PARAMETERS OF THE RESEARCH STUDY

Two parameters were used in this study to ascertain the effect of *Gelsemium sempervirens* 200CH on anxiety and urinary cortisol levels in students undergoing a test.

The first parameter was the measurement of state anxiety. The second parameter was the measurement of urinary cortisol levels over a 24 hour period. Trait anxiety was not considered as a parameter although it was analysed and discussed. Trait anxiety reflects the personality of the subject and therefore would not have changed the outcome of the study. The correlation of these two parameters was determined in order to determine whether *Gelsemium sempervirens* 200CH had a physiological influence on anxiety and urinary cortisol.

5.2. DISCUSSION OF RESULTS

5.2.1. State anxiety

The anxiety levels of the control group were relatively low during the first round, because no test was scheduled on that day or during that week. During the second round, when the students wrote their test, there was a slight increase in anxiety levels.

When comparing the anxiety levels of the experimental group during the first and second rounds; the experimental group showed a slight decrease in anxiety levels, but this decrease was not statistically significant.

5.2.2. Trait anxiety

The control group showed no change in anxiety levels during the first and second round. However, the experimental group showed a slight decrease in trait anxiety during the second round.

5.2.3. Cortisol

The levels of cortisol in the control group increased during the second round. The experimental group showed a decrease in cortisol levels during the second round. The difference between the cortisol levels of the control group and that of the experimental group showed a statistically significant difference.

5.2.4. Summary

When comparing state anxiety and cortisol levels, there is a correlation between the decrease in state anxiety and cortisol levels of the experimental group (Refer to Table 4.4.1.) and an increase in state anxiety and cortisol levels of the control group (Refer to Table 4.4.1.).

The results of this study correlates to a study conducted by Prussner, *et. al.*, (1997:616-622), which suggested that there is an association between cortisol responses after exposure of psychosocial stress. Both these studies showed an increase in cortisol levels after exposure to psychological stress or anxiety. In another study done by Malarkey, *et. al.,* (1995:499-508) it was found that when students wrote an exam, levels of cortisol increased significantly from the baseline level when they experience the most stress. Vedhara, *et. al.,* (2000:535-549) also stated that levels of anxiety decreases when cortisol levels decrease. Prussner, et. al., (1997:616) suggested that the trait component of cortisol stress response need to be determined in order to reveal consistent associations between personality traits and cortisol stress responses.

CHAPTER SIX

6. RECOMMENDATIONS AND CONCLUSIONS

6.1. RECOMMENDATIONS

This study was an excellent learning experience for the researcher, however, a few shortcomings were identified in this study. Firstly, the sample group was too small. It is recommended that should further studies be carried out in this research field, a larger sample group should be used. If a larger sample was used, it might be possible that the changes that were not significant might increase to show a significant change. There were many dropouts in this study, if a larger group was used, this might not have had such a significant effect.

Secondly, *Gelsemium sempervirens* is commonly used in clinical practice to treat anxiety, and are considered specific for this condition. There are many other homoeopathic remedies which may be used to treat this condition, including *Kalium phosphoricum, Argentum nitricum, Arsenicum album*, and *Lycopodium* to mention but a few of the hundreds listed in the repertory (Schroyens, 1998:14). Because homoeopathy is a very individualised form of treatment, a careful medical and homoeopathic evaluation is essential for each patient. To find the correct "similum" remedy for each subject is essential for the results to be most effective. *Gelsemium sempervirens* was not the similimum remedy for most of the subjects, which might be a setback for the research. The researcher believes that if further studies are attempted in this field, the similimum remedy for each individual should be used after a thorough homoeopathic case study was taken to assess each participant.

Another important factor, which might influenced the study, is the fact that the study included subjects from a wide range of different socio-economical backgrounds. Different factors might have an influence in the way that student

cope with anxiety. The domestic situations and socio-economical backgrounds were not taken into account. The following factors are important to consider if further studies were conducted: use of recreational drugs, nutritional inadequacies, lack of finances (where the student could not purchase the prescribed textbooks or had to hold down a job, which allows less time for study and relaxation), inefficient study methods, language problems especially where English is not the home language, an inability to identify important information, and poor communication skills between the student and the lecturer. The broader picture should be looked at when prescribing a remedy.

The potency and frequency of the remedy should be evaluated. It is recommended that either a combination of potencies should be used or that the subjects should take the remedy over a longer period of time.

It is questionable whether the students complied to the guidelines given to them beforehand. With regard to the anxiety inventory, the questions of the inventory may not have been fully understood by some of the participants, because English is not their first language. Some might not have been honest when they completed the inventory. It might be that they did not take the research study serious enough to comply. It is uncertain whether the students took their remedies, as it was explained to them. Although the urine samples was taken over a 24-hour period, all the nocturnal fluctuations of cortisol were included in the sample. But it is uncertain whether the students collected all their urine during that period.

For further studies, the researcher recommends that because the remedy decreased anxiety when the students wrote a test, other anxiety induced situations should also be considered, for example for public speakers, people going for a job interview, etc. Including students' test results can also expand the study, so that a correlation between anxiety levels, levels of urinary cortisol and test marks can be determined.

With all of the above taken into account, it is important to identify and diagnose feelings of anxiety, but it is also important to identify the cause of anxiety, whether physical, psychological or emotional. The researcher suggests that if another study is to be conducted in this research field, socio-economical background and domestic situations should be looked at. This in itself could lead to great anxiety. The use of recreational drugs and nutritional inadequacies may influence the way that the subjects cope with anxiety.

It is important to take note of the fact that the remedy did work (even though not statistically significant), because this may pave the way for finding treatment for anxiety in at least some patients, that could possibly replace allopathic medicines with all its undesirable side effect.

6.2. CONCLUSION

The purpose of this study was to evaluate the effect of a homoeopathic remedy on levels of anxiety and urinary cortisol, by using the State-Trait Anxiety Inventory and the Beckman Access Immunoassay System respectively.

Significant differences were found between the control and the experimental groups. The levels of state anxiety decreased in the experimental group, but it increased in the control group. The difference however, was not statistically significant. The levels of urinary cortisol showed a statistical significant difference. The cortisol levels of the control group increased, whereas the cortisol levels of the experimental group decreased remarkably.

Taking all the above into account, it is clear that *Gelsemium sempervirens* caused a decrease in levels of anxiety in relation to a decrease in urinary cortisol.

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APPENDIX A: Subject information and Consent form

As a student you are aware of anxiety, be it from first hand experience or from listening to fellow students talking about anxiety. A little anxiety is a good thing but as you may well know, too much can be detrimental to your mental and physical health. We are asking you to participate in a study aimed at helping to control and reduce the amount of the stress hormone cortisol. This hormone is responsible for feelings of nervousness and anxiety as well as contributing to depleting your immunity to infection.

If you participate in this study, you need to be older than 18 years of age. You will be required to give us two 24-hour urine samples 15 days before and on the day of your test. Each volunteer will be issued with a numbered, empty sample bottle just before the testing begins. The sample bottles will be stored in the TWR Health Clinic for you to use at your discretion. The sample bottles will be taken home with you and returned to us the next morning. On the days that your cortisol levels are tested you will also be required to complete a 10-minute standardised psychological test to measure your perceived level of nervousness and anxiety.

As this is a double blind, placebo-controlled fully randomised study, no names will be involved and results will be issued to volunteers on the basis of their number being used during the research. Half the volunteer group will receive the placebo and the other half the homoeopathic remedy. Neither the researcher nor the participants will know who is receiving a placebo or who is receiving the actual complex homoeopathic remedy.

Participation in this study is voluntary and you are free to refuse to participate or withdraw from participating at any time throughout the study. A signed copy of this consent form will be made available to you. We have explained fully what is expected of you and answered all your questions.

Date: _____ Researcher: _____

I have been fully informed as to my rights and as to the procedure to be followed in this study. I understand that I am free to withdraw my consent at any time. I know that any questions I have will be answered fully.

Date: _____ Participant: _____

APPENDIX B: Procedure on 24 – hour urine collection

1. On the day before the collection of the urine, each subject will be issued with a two-litre urine collection bottle. Each of the subjects will receive a number, which will be displayed on the collection bottle.

2. On the morning to the research, the first urine of the day should be discarded. All the following urine up to and including the urine produced just after the 24 hours should be collected in the bottles provided.

3. The collection bottles will be stored at the TWR Health Clinic whilst the subjects attend lectures. At the end of the day, the subjects must take their sample bottles home for the overnight collection of urine.

4. The collection bottles should be returned the morning after to the TWR Health Clinic. Where the researcher will take the collection bottles to the laboratory.

The day before the test, the subjects will again receive their collection bottles as pointed out in points 1 to 3. If the subjects need to urinate during the test, the researcher will be at the room with smaller, clearly marked collection bottles, with corresponding numbers, which will be used and after will be discarded into the larger collection bottles.

APPENDIX C: Procedure on how to take the medication

You have been issued three powders. The powders should be taken in the following manner:

- The first powder should be taken the morning before your test.
- The second powder should be taken the evening before the test.
- The last powder should be taken the morning of the test.

These powders should be taken on an empty stomach, the mouth should be clean. Just put the powder in your mouth and let it dissolve.

APPENDIX D: Raw data

NR.	State anxiety (First round)	State anxiety (Second round)	Trait anxiety (First round)	Trait anxiety (Second round)	Cortisol/24 hour (First round)	Cortisol/24 hour (Second round)
8	52	53	57	49	243	283.4
11	54	74	50	57	188.1	712.38
16	56	53	58	57	178.88	527.5
26	55	67	54	53	263.64	331.55
28	65	0	57	0	439.2	0
32	44	0	52	0	337.4	245.1
37	43	0	55	0	147.16	312
40	53	0	54	0	250.08	0
43	53	0	48	0	178.71	956
46	67	0	55	0	236.46	317.05
					nmol/day	nmol/day
Mean value	54.2	61.75	54.0	54.0	246.26	460.62

Table 1: Raw data of the control group

NR.	State anxiety (First round)	State anxiety (Second round)	Trait anxiety (First round)	Trait anxiety (Second round)	Cortisol/24 hour (First round)	Cortisol/24 hour (Second round)
1	51	85	53	52	616	112.5
19	51	44	60	51	448.25	69.6
20	56	46	61	41	465.3	182
21	65	67	69	44	1089.14	108
22	74	0	78	0	0	30
23	63	50	71	68	258.4	84
25	47	53	42	47	85.26	7.41
29	51	41	40	38	387.1	173.6
33	57	0	57	0	824	67.2
38	61	0	64	0	175.8	110.6
					nmol/day	nmol/day
Mean value	57.9	55.14	59.5	48.71	483.25	94.49

Table 2: Raw data of the experimental group