The relative efficacy of Evening Primrose oil and low Homoeopathic potency Gamma Linolenic acid in the management of Attention Deficit Disorder (ADD) and Attention Deficit Hyperactivity Disorder (ADHD) in males age 5-13.

By

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I, Justin Brett Middleborough, do hereby declare that this Dissertation represents my own work both in conception and execution.

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I WOULD LIKE TO DEDICATE THIS TO THE MEMORY OF MY FATHER

JOHNNO, AND TO MY MOTHER CAROL AND

SISTER SHELLEY FOR ALL THEIR LOVE AND

SUPPORT THROUGH ALL MY YEARS.

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ABSTRACT

The aim of the study was to evaluate the relative efficacy of homoeopathically prepared Gamma Linolenic acid (GLA) in comparison to supplementation of GLA, in the form of Evening Primrose oil, in the treatment of ADD/ ADHD with regard to inattention, impulsivity and hyperactivity. It was hypothesised that both the homoeopathically prepared GLA and the Evening Primrose oil would result in a substantial improvement in boys diagnosed with ADD/ ADHD and thus lead to their recommendation as an alternative to Methylphenidate hydrochloride (Ritalin®) in the treatment of these disorders. The use of homoeopathically prepared GLA was a first and was based on the rational used by the Heel company and the Schussler method of tissue salt therapy where dilutions of chemicals or compounds are used to correct physiological deficiencies, their mechanism of action is not fully understood but it is believed that in these diluted states the homoeopathically prepared substances are believed to work on a energetic level rather than a physical level. Both of these methods rely on chemicals or compounds, which have been successively diluted and potentised, i.e. prepared homoeopathically. In order to gain a similar effect the GLA was prepared in the same manner and not just diluted.

This study was a clinical trial, in which a placebo control group was compared with two experimental groups. The study was undertaken over a period of one year. Thirty ADD/ ADHD children attending schools in the greater Durban area were recruited. The thirty children chosen were in some cases taking Ritalin, prescribed by their doctors, and in other cases no form of treatment was being used after parents had either tried their children on Ritalin or had been too afraid to try Ritalin after hearing of its adverse side-

effects. The joint-supervisor randomly allocated the 30 children into three groups. A placebo group (n = 10), a group receiving supplementation using Evening Primrose oil (n = 10) and a group receiving treatment of homoeopathically prepared GLA (n = 10). Each of the subjects was treated and observed over a period of four weeks.

Prior to and at weekly intervals during the four weeks of treatment each subject was assessed using the ADHD Rating Scale –IV questionnaire. Statistical analyses were performed on these questionnaires using non-parametric tests.

The intra group analyses revealed that no statistically significant differences occurred in either of the groups. The inter group analyses revealed a significant improvement in the Evening Primrose oil group with regards to inattention scores between the first and third and first and fifth questionnaires compared to those in the other two groups. A significant improvement was also noted in the total score for the Evening Primrose oil group between first and third questionnaires compared to the other two groups.

Footnote

At this stage it must be stated that most of the research which was done in the early 80's is still valid today. Research into the link between GLA deficiency and ADD/ ADHD began in the early 80's and has not been as comprehensive as the research into neurological involvement. For these reasons many of the references used are relatively old, sometimes twenty years or more, however the fundamental principles that are the basis for these references are still valid today.

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DEFINITION OF TERMS AND ABBREVIATIONS

I. **Atopic** – relating to or marked by atopy (Stedmann's Medical Dictionary, 1995).

II. **Atopy** – a genetically determined state of hypersensitivity to environmental allergens, includes common allergic conditions like asthma, atopic eczema and hayfever (Stedmann's Medical Dictionary, 1995).

III. **Attention Deficit Hyperactivity Disorder (ADHD)**– a disorder of attention and impulse control with specific DSM-IV criteria, appears in childhood and may continue through to adulthood though it usually subsides during adolescence. Hyperactivity may be a feature but is not a requirement for diagnosis (Stedmann's Medical Dictionary, 1995).

IV. **Dihomo-gammalinolenic acid (DHGLA)**

V. **Essential Fatty acid (EFA)**– any long chain monobasic organic acid required for normal functioning of the human body and which must be obtained from a food source (Stedmann's Medical Dictionary, 1995).

VI. **Evening Primrose oil** – oil derived from the seed of the Evening Primrose plant (*Oenothera biennis*) (Chevallier, 1996).

VII. **Gammalinolenic acid (GLA)**

VIII. **Hyperactivity** – muscular activity which is exaggerated considered to be inappropriate in terms of situation and excessive in duration (Picton, 1997). The hyperactive child shows a high level of mobility and inappropriate behaviour so that he or she is in constant conflict with the social environment (Kapp, 1991)

IX. **Inattention** – a lack of attention or concerted effort in situations, which require extended concentration like performing a monotonous task such as reading or writing (Serfontein, 1990).

X. **Impulsivity** – sudden behaviour which is acted out without any thought with regards to consequences of the behaviour (Picton, 1997).

XI. **Pillules** – Minute pills in pellet form of a more or less spherical shape. Made of cane sugar ($C_{12}H_{22}O_{11}$). The size used in this study was a 30 from the number of millimeters taken up by 10 pillules in a straight line. Used homoeopathically as the vehicle for dispensing the medicines with which they have been impregnated (Gaier, 1991).

XII. **Prostaglandin** - any of a class of physiologically active substances present in all tissues of the body with a broad range of effects which are local rather than systemic. Examples of effects are vasodilation, vasoconstriction, smooth muscle control and control of membrane permeability of cells. The basic structure is prostanoic acid, a twenty carbon fatty acid, with side chains of varying amounts of oxidation and unsaturation (Stedmann's Medical Dictionary, 1995).

XIII. **Prostaglandin E1 (PGE1)**

NOTE ON THE REFERENCES

Research into the link between GLA deficiency and ADD/ ADHD began in the early 80's and has not been as comprehensive as the research into neurological involvement. A lot of the research that was done in the early 80's still stands true today. For these reasons many of the references used are relatively old, sometimes twenty years or more, however the fundamental principles that are the basis for these references are still valid today.

CHAPTER 1

2.1.2 INTRODUCTION

A large proportion of the behavioural problems presenting in paediatric practices are attributed to Attention Deficit Disorder, with or without Hyperactivity (ADD/ ADHD). The total number of children affected with this disorder has been estimated at being between three and five percent. Epidemiological studies have shown that this figure is true for Southern Africa but that the actual figure may be higher due to the fact that many children in rural settings do not have access to psychological testing. In fact the teacher awareness in these areas is very low and as a result many children are not referred for proper testing (Robertson, Allwood and Gagiano, 2001).

There is a greater ratio of boys to girls affected with this disorder, some conservative estimates put this ratio at 2:1 while others put it higher at as much as 8:1 (Picton, 1997). The reason for this can be attributed to at least two factors; girls tend to be less active and aggressive than boys are and so they are less likely to be noticed as disrupting the rest of their class. It is the hyperactive component which is most often identified, presumably a fair number of boys are mistakenly identified as being sufferers due to poor diagnosis from doctors whilst many girls are not identified as their hyperactivity tends to be less of a factor.

Some researchers have established a link between GLA deficiency and ADD/ ADHD, this link is the basis for this research project and will be explored more thoroughly in the following chapters (Medical Hypothesis, 1981; Graham J., 1993).

The Gamma Linolenic acid (GLA) requirements of boys have been shown to be higher than that of girls and so they are more likely to be affected from this particular cause of ADD/ ADHD (Graham, J., 1993). The fact that the incidence of ADD/ADHD is higher amongst boys than girls (Picton, 1997) and the fact that the GLA requirements of boys is higher than that of girls (Graham, 1993) supports the theory that a GLA deficiency could be an important aetiological factor in ADD/ADHD.

There are three postulated reasons why GLA may become deficient. These will be discussed in more detail in the following chapters but briefly they are as follows:

1. ADD / ADDH children could have an inherent intestinal problem which leads to difficulty with absorption of Essential Fatty Acids (EFA's) (Medical Hypothesis, 1981).

2. ADD/ ADDH children could have a metabolic requirement for higher levels of EFA's than normal due to a genetic difference (Medical Hypothesis, 1981; Graham J., 1993).

3. ADD/ ADDH children may have a defect in their metabolism of EFA's. This is substantiated by the fact that most EFA in our diets comes in the form of cis-linoleic acid. This is then converted by enzymes into Gamma-linolenic acid and then into dihomo-gammalinolenic acid (DGLA) before it is converted into Prostaglandin E1 (PGE1), which is the usable form (Galli and Simopoulos, 1989). The initial step of this sequence is catalysed

by the hormone delta-6-desaturase, which is most susceptible to blockade.

There is much controversy surrounding the diagnosis of ADD/ ADHD yet all of those involved in the treatment of these children agree that the numbers of affected children warrants serious attention. It must be understood that it is during the formative years of a child's education that the most progress is made in intellectual development and the learning of principles of society, this is the same period where ADD/ ADHD becomes most prevalent. Any factor that hinders a child's progress in this period has a veritable influence on the rest of society as it can lead to delinquency in later years and hence dependency on welfare structures (Picton, 1997).

Currently Methylphenidate hydrochloride is the most popular drug used in the treatment of ADD/ ADHD. Due to increasing concerns about its safety, many parents have opted to try natural approaches first in an effort to eliminate the risk of side effects experienced by users of medications like Ritalin® (Holford, 1997). Homoeopathy and supplementation with natural products like Evening primrose oil are two natural approaches, which are first and foremost safe and can be used in conjunction with one another. As yet very little research has been done on establishing the efficacy of these two approaches and thus was the primary aim of this research project.

Homoeopathy is a very diverse method of treatment, which ranges from classical prescriptions to clinical prescribing. The medicines are substances of both organic and in-organic nature that are administered in small doses after the raw material has been

potentised. Potentising is a process whereby the raw material is successively diluted and shaken, this removes the possibility of toxicity and increases the healing potential of the substance (Gaier, 1991).

Homoeopathically prepared remedies can be used to address deficiencies within the body. Two methods are used today which rely on homoeopathically prepared remedies applied in a different manner than the usual classical or clinical prescription methods. The approach which was chosen for this particular research is derived from the Schussler theory of biochemical tissue salts and the Heel® theory of homotoxicology. It relies on addressing a single problem within the individual, like a deficiency, and then administering a substance, which should correct this deficiency. The remedy that was used was prepared in a homoeopathic manner but the method of prescription is not according to the usual law of similars as in classical Homoeopathy. In this research project GLA deficiency was identified as one of the possible causes of ADD/ ADHD and the prescription that was used was chosen for its probable effects on countering this deficiency. Schussler Tissue salts are used in a similar manner to correct deficiencies of minerals in the body, for instance tissue salt number four, Ferrum Phosphoricum, is used to correct deficiencies of Iron in the body (Gilbert, 1989).

Heel products have been researched and shown to be capable of reducing deficiencies by administering the deficient substance in low dilutions as homoeopathically prepared medicines (Biotherapeutic index, 2000). The rationale behind these treatments is that the treatment is not on a physical level, rather the homoeopathically prepared medicines have

an energetic nature which stimulates the body and allows it to correct the deficiency using its own abilities. This approach is not limited to Iron deficiencies but is also applied to deficiencies of Calcium, Magnesium, Sodium Chloride and Vitamin B12. Homoeopaths around the world use these methods as fundamentals when treating basic deficiencies in the human body (Gilbert, 1989).

Therefore the aim of this research was to demonstrate the benefit of supplementation with GLA or a homoeopathic preparation of potentised GLA, intended to correct GLA deficiency, as possible alternatives to the use of Methylphenidate hydrochloride. As the research was based partly on the principles of homotoxicology and Tissue Salt therapy it was decided that the GLA should be prepared homoeopathically and not merely diluted, this would enhance the energetic effects of the substance as opposed to merely diluting them.

Given the correspondence between GLA deficiency symptomatology and that of ADD/ADHD, GLA deficiency is proposed as an aetiological factor in ADD/ADHD (Graham, 1993). The aim of this double-blind, placebo-controlled study was to determine the efficacy of homoeopathically prepared GLA (6CH) as compared to GLA supplementation (material dosage) in the treatment of ADD/ADHD. It was hypothesised that treatment with homoeopathically prepared GLA would assist in correcting the underlying GLA deficiency; this is based on the principals of homotoxicology i.e. the GLA in homoeopathic potency does not act on a physical level as the dilution is too low

to have any possible benefit as a supplement, but rather once it is potentised it becomes active on an energetic level stimulating the body's own ability to correct the deficiency (Biotherapeutic Index, 2000). Similarly the use of minerals in low homoeopathic dilutions (Biochemical Tissue Salt Therapy) have been shown to correct deficiencies of the corresponding minerals in their physiological concentrations (Gilbert, 1989).

Further it was hypothesised that treatment with homoeopathically prepared GLA could reverse GLA deficiency more effectively that GLA supplementation alone; it is unlikely that GLA deficiency in ADD/ADHD children is due to inadequate intake but rather due to deficient absorption, genetically related abnormal GLA metabolic requirements and defective EFA metabolism (Medical Hypothesis, 1981; Graham, 1993).

CHAPTER 2

REVIEW OF THE RELATED LITERATURE

2.1.1 ADD/ADHD - EPIDEMIOLOGY

In this literature review all aspects of ADD/ ADHD relevant to the research will be investigated. ADD/ ADHD is one of the most commonly diagnosed disorders of childhood development (Kendall and Hammen, 1995;Venter, 1996). It is believed to affect between 3-5% of all children of school age and although it also affects adults and adolescents, the figures here are not available (DSM-IV, 1994). Some reports claim that between 5-15% of all boys are affected with this disorder (Picton, 1997). The values for females are often under reported due to the fact that they go undiagnosed as their symptoms are attributed to emotional problems common in young girls (Kendall and Hammen, 1995) and they are less aggressive and active than boys, which makes them less noticeable (Picton, 1997). The ratio between boys and girls is commonly given as 4: 1 or even 9:1, male: female (Barkley, 1990; Zillmer and Spiers, 2001).

2.1.2 ADD/ ADHD - PATHOPHYSIOLOGY.

The physiology of the disorder is unclear but there are a number of theories, which attempt to explain either part of or the sum of the processes involved. One of the earliest theories was that concerning a neurological origin, although to begin with the theory was broad in its definition, meaning children were labelled as having minimal brain dysfunction or even brain damage, psychologists today now recognise that many factors are involved in the development of this disorder. These factors can include inferior

teaching methods, incompetent teachers, intrafamilial stress and even cultural pressures, which all exert a negative impact on the child's behaviour and progress (Engelbrecht, Kriegler and Booysen, 1996). These factors may co-exist with one another and may or may not include a physiological component

It has been postulated that an area in the brain, which is responsible for inhibiting the activity and activating attention levels is underactive (Venter, 1996). Some researchers have been more specific and have labelled the areas thought to be involved as the reticular activating system (attention), frontal lobes (voluntary attention) and the temporal-parietal regions (involuntary attention). Subsequent research has failed to prove these theories conclusively and it is now believed that brain impairment may only be present in those with pervasive ADHD (Smith, 1970; Zillmer and Spiers, 2001). The disruption of normal function of the frontal-basal ganglia has also been postulated. These ganglia are sub-cortical nuclei situated below the frontal lobes. Until recently it was believed that these ganglia were involved in motor control only, new research has indicated that they may have a role to play in cognitive functioning. The exact nature of this role is unclear but neuroscientists believe it may be an inhibitory function that serves to control the frontal lobes (voluntary attention). Positron emission tomography (PET) of children affected with ADHD has shown decreased blood flow to the basal ganglia as well as a reduction in the size of the basal ganglia. Findings have not been altogether conclusive but support for the theory has been found in studies that show that stimulant medications, like Ritalin®, actually increase the amount of blood flowing to the basal ganglia. These findings offer a partial explanation for the aetiology of ADHD as well as

helping to explain the pharmacological action of Ritalin® (Zillmer and Spiers, 2001). Another proposal is that there is an abnormality with regards to dopamine metabolism in areas in the brain (Rapport, Quinn and Lamprecht, 1974: Levy, 1991).

Lately researchers have found a correspondence between the symptoms of ADD and a deficiency of Gamma-linolenic acid (Graham J., 1993; Van der Merwe, 2000.). Due to this correspondence of symptoms it has been theorised that it is actually a deficiency of GLA that gives rise to the ADD/ ADDH disorder in a large percentage of cases (Efamol, 1980; Medical Hypothesis 7, 1981; Graham J., 1993). The mothers of the affected children have been shown to have a tendency towards pre-menstrual tension (PMT) and often suffer from migraines, there is also a tendency in the families of sufferers for allergies, asthma and hay fever (Picton, 1997). These symptoms correspond with the symptoms seen in GLA deficiency.

Diagnosis is a problem as it has been shown that many children are not identified or otherwise falsely identified by their paediatrician or doctor for a number of reasons. Testing of children is often limited and not comprehensive enough, case histories may not be detailed enough and often the influence of a teacher or school is enough to encourage a doctor to prescribe stimulant medication (Sue, Sue and Sue, 1994; Picton, 1997; Oltmanns and Emery, 1995). The most commonly used diagnostic method is from the Diagnostic and Statistical Manuel – IV (1994) (Appendix H)

2.1.3 AETIOLOGY

The symptoms characteristic of this disorder, hyperactivity, short attention span and

impulsiveness are thought to suggest central nervous system involvement. As a result many conditions which are believed to cause neurological impairment like lead poisoning, chromosomal abnormalities and foetal alcohol syndrome have been linked or proposed as possible aetiologies of ADD/ ADHD (Balch and Balch, 1990; Hynd *et al.*, 1991). Many other possibilities have been proposed including certain foods or food additives, sugar, colourants and preservatives (Sue, Sue and Sue, 1994; Holford, 1997; Picton, 1997). Variables, which are specific for each family may be indicated although it is as yet unclear whether these are genetic, environmental or a combination of the two (Sue, Sue and Sue, 1991). There has recently been research into the possibility that there is a higher incidence of ADD/ ADHD amongst first degree relatives of sufferers as well as a higher prevalence amongst monozygotic twins, the results have indicated a possible genetic transmission (Robertson, Allwood and Gagiano, 2001).

A neuro-chemical cause has been investigated and abnormalities in the dopamine metabolism of schoolage children, who were affected, were found (Rapport, Quinn and Lamprecht, 1974: Levy, 1991). Hynd *et al.* (1991) displayed with MRI techniques that a difference between the corpus callosum morphology of children affected by the disorder and those of normal children exists but results were not consistent with all those diagnosed as affected. Another proposal was that affected children have a dysfunction in the right sided frontal striatal system (Benson, 1991). Generally the scientists who make these assertions agree that there is some form of dysregulation of the central noradrenergic systems and that central dopaminergic and peripheral adrenergic systems probably also play a role (Robertson, Allwood and Gagiano, 2001). Dysfunction of the

frontal-basal ganglia circuit has also been implicated in a percentage of patients, still neuroscientists are unsure whether these abnormalities are acquired, congenital or inherited (Zillmer and Spiers, 2001).

Social factors have been implicated by Richman, Stevenson and Graham (1982), who decided after research that children who grow up in poor social conditions where inadequate housing and lack of financial security are prevalent, were more likely to display behavioural difficulties. Children who are raised with unskilled parenting are not given consistent and predictable limit setting, they are therefore poorly equipped to deal with the demands of a structured school day (Robertson, Allwood and Gagiano, 2001)

Parental behaviour was indicated as a possible cause by Graham, P. (1986), who showed that mothers of hyperactive children tend to be unresponsive to the child's demands, he proposed that the child's hyperactivity is merely an attempt to elicit a response (Graham, P., 1986; Picton, 1997. However this explanation fails to account for the fact that the mothers behaviour may be as a result of enduring years of abnormal behaviour. Abused children are also known to develop classical symptoms of ADD/ ADHD, clearly these children are a minority but with reports of growing figures of abused children this is an ever increasing problem which cannot be ignored (Oltmanns and Emery, 1995).

Commonly these different proposed causes are found in combination in affected children and as such no single aetiology can be defined, occasionally all are absent making the aetiology idiopathic (Picton, 1997).

GLA deficiency is another proposed aetiology which became the focus of this research. There is a large correlation between symptoms of ADD/ADHD and those of GLA deficiency. In order to treat GLA deficiency it needs to be understood how an individual can become deficient in GLA. GLA can be absorbed directly into the body but for the most part it is converted internally from EFA's which are more abundant in the diet. There are three postulated reasons at present:

1. ADD / ADDH children could have an inherent intestinal problem which leads to difficulty with absorption of Essential Fatty Acids (EFA's) (Medical Hypothesis, 1981).
2. ADD/ ADDH children could have a metabolic requirement for higher levels of EFA's than normal due to a genetic difference (Medical Hypothesis, 1981; Graham J., 1993).
3. ADD/ ADDH children may have a defect in their metabolism of EFA's. This is substantiated by the fact that most EFA in our diets comes in the form of cis-linoleic acid. This is then converted by enzymes into Gamma-linolenic acid and then into dihomo-gammalinolenic acid (DGLA) before it is converted into Prostaglandin E1 (PGE1), which is the usable form (Galli and Simopoulos, 1989). The initial step of this sequence is catalysed by the hormone delta-6-desaturase, which is most susceptible to blockade.

2.1.4 PRINCIPAL CHARACTERISTICS OF ADD/ ADHD

Clinical picture and diagnosis.

The clinical picture of a child suffering from ADD/ ADHD is variable but usually

consists of one or more of the following symptoms: -

- Hyperactivity which, is the aspect that is most noticeable to adults is really motor hyperactivity. The hyperactivity is found in the child in a variety of situations including sleep (Oltmanns and Emery, 1995). It is however far more noticeable in structured situations, like a classroom, than in an unstructured situation like a playground (Barkley, 1988, 1990). It is partly because of this that ADD/ ADHD is only diagnosed when the child first attends school. The hyperactivity can be influenced by certain situations, which leads to a difficulty diagnosing the disorder. In one study it was found that only 20% of children with ADD/ ADHD were overly active during examination in their paediatrician's office (Sleator and Ullmann, 1981; Zillmer and Spiers, 2001).
- Inattention is noticed when children have a problem with sustained attention, it is sometimes referred to as sensory hyperactivity due to the distractibility so prevalent in these children (Kapp, 1991). Numerous studies using the *continuous performance test* have been documented. The test requires the children to monitor and respond to numbers and letters on a computer screen, in hyperactive children the ability to do this quickly deteriorates (Douglas, 1983) (*continuous performance test* is documented in Oltmanns and Emery, 1995). The hyperactivity has been shown not to be a consequence of inattention (Barkley, 1990).
- Impulsivity has been less studied than the other two symptoms. It is characterised by behaviour where action is taken without any indication of thinking of consequences.

The general symptoms that are really sub-groups of these primary symptoms can be

classified according to area of effect (Picton, 1997).

I. Co-ordination

- Gross co-ordination: clumsy, tripping, colliding with objects, inability to play sport.
- Fine co-ordination: poor hand-eye co-ordination, difficulty with buttoning, tying, fastening, drawing and cutting.
- Speech difficulties: stuttering, stammering and pronunciation difficulties.

II. Attention

- Short attention span.
- Lacking in selective attention.
- Very distractible.
- Unable to concentrate.
- Tendency to daydream.

III. Learning difficulties and disabilities.

- Auditory/ memory deficits – difficulty remembering details.
- Visual/ memory deficits – difficulty copying from the blackboard.
- Poor comprehension
- Disturbance in optical orientation (mistaking b for d – dyslexia)
- Difficulty in reasoning (word definitions and maths problems).

IV. General

- Maturational lag – emotionally, physically and academically immature.
- Poor planners, lack organisational skills.
- Often losing things.
- Do not complete tasks.
- Cannot tolerate change.
- Can not be diverted from action even if the consequences are dangerous, as they can not comprehend these.
- Punishment seems to increase their frustration leading to increased tantrums.
- Pyromania.
- Perseveration – meaningless repetition of an action.

5. Physical characteristics.

- Often suffer from colic as babies.
- Usually skinny.
- Allergies or sensitivity to many foods and substances.
- Eczema and other skin disorders.
- Unquenchable thirst.
- Abnormal appetite.

Not all ADD children display hyperactivity, for this reason many that are hypoactive may

be undiagnosed or misdiagnosed. Hyperactive symptoms tend to decrease with age although not always (Picton, 1997).

Girls tend to show less symptoms of aggression and attract less attention and so may remain undiagnosed, this may explain why the disorder is more prevalent in males (Sue, Sue and Sue, 1994; Picton, 1997).

2.2.1 TREATMENTS

The standard medical treatment varies according to each child but it generally incorporates the administering of a psychostimulant or similar drug if the former is ineffective. Methylphenidate (Ritalin®) is the drug of choice, however it is ineffective in up to 30% of all sufferers. The drug is effective in improving concentration and memory and to control frustration and anger (Sue, Sue and Sue, 1994; Picton, 1997).

Other medications, which are used in place of methylphenidate, are:

- Dextroamphetamines (Dexedrine® and Eskatrol®) – more severe side effects , habit forming and not recommended for children under twelve years old.
- Pemoline (Cylert®) – less effective than methylphenidate and takes up to one month before maximum effect is noted, can be habit forming and often leads to insomnia.
- Fencamphamine – also contains multivitamins and is generally indicated in the hypoactive ADD child who is more lethargic.
- Imipramine (Tofranil®) – commonly used in children who react badly to methylphenidate especially where motor disorders like tics or epilepsy

appear. This medication can have severe side effects including cardiac arrhythmia and takes three weeks to begin effect.

- Clonidine – mainly effective in hyperactivity-impulsivity type, this drug is typically used as an anti-hypertensive however its calming effects have been useful in conditions of overactivity. It should not be given to children below the age of twelve years.
- Thioridazine (Mellaril®) – may be given to toddlers too young for Ritalin®, it can over sedate the child leading to learning problems. This drug is a tranquilliser which reduces anxiety and agitation.
- Haloperidol – useful for overactivity however it can lead to severe movement disorders. This drug is an antipsychotic tranquilliser that reduces severe anxiety and agitation
- Sulpiride – an antipsychotic sometimes used to treat the side effects of Ritalin®. Normally it is indicated for the relief of symptoms in Schizophrenia treatment where it increases an apathetic and withdrawn patient's awareness.
- Carbamazepine (Tegretol®) – is an anticonvulsant and anti-epileptic drug. Epileptic patients are unable to use stimulant medication like Ritalin® and so these symptoms are first controlled before stimulant medication is administered.
- Sodium Valproate (Epilim®) – mainly indicated in petit-mal epilepsy this drug is useful for controlling seizure disorders and epilepsy before stimulant medication is administered.

(Griffith, 1989; Morton and Hall, 1995)

Although these drugs have all been used their side-effects are either more severe or their efficacy less than methylphenidate (Picton, 1997). Methylphenidate is contraindicated in a number of conditions including anxiety, thyrotoxicosis, tachyarrhythmias, severe angina pectoris and glaucoma. It is not advisable to be used in children younger than 6 years old or in patients with a history of seizures or uncontrolled epilepsy (Internet 2).

Medical treatment may be in conjunction with behavioural therapy, counseling and special diets although these do not form the mainstay of medical treatment (Oltmanns and Emery, 1995).

2.2.2 WHAT IS METHYLPHENIDATE HYDROCHLORIDE (RITALIN®)

Ritalin® or Methylphenidate hydrochloride is a schedule seven drug with a pharmacological classification of A 1.2 Psychoanaleptic (antidepressant). Its action is described as a stimulant effect on the central nervous system. It is indicated for the treatment of ADHD and Narcolepsy. Ritalin® is rapidly and almost completely absorbed however due to an extensive first–pass metabolism through the liver the actual availability amounts to an average of 30% of the dose. Dosage varies with individual patient needs and response, the average dose is given as 20-30mg daily but the actual range is from 10mg up to 60mg per day (Novartis, 1999).

2.2.3 THE EFFECTS OF METHYLPHENIDATE HYDROCHLORIDE

Methylphenidate hydrochloride is classified as a Psychoanaleptic drug (antidepressant) with a mode of action described as a stimulant effect on the central nervous system (Novartis, 1999). The mode of action is not completely understood but it is presumed to

activate the brain stem arousal system and cortex thus producing its stimulant effect (Internet 2). An increase in blood flow to the frontal-basal ganglia has also been shown, this region is believed to have an inhibitory or controlling effect on the frontal lobe (voluntary attention) (Zillmer and Spiers, 2001). The drug is rapidly absorbed into the body and peak plasma concentration levels were observed after 2 hours on average. The effects are usually first noted 20-30 minutes after administering the medicine. The effects normally last for 4-6 hours, although a sustained release form of the drug has been developed it has not proven to be as effective in controlling symptoms. The drug is rapidly metabolised and is non-accumulative in the body (Griffith, 1989; Venter, 1996). Standard medical treatment recommends drug holidays of 2-3 days to clear the body of all the drug metabolites. Poling, Gadow and Cleary (1990) found that nearly one third of ADHD patients who were treated with Ritalin® showed no positive results or their condition was worsened while taking medication (Sue, Sue and Sue, 1994).

2.2.4 SIDE EFFECTS OF METHYLPHENIDATE HYDROCHLORIDE

Despite the efficacy of the drug it has become notorious for its side effects. There are many documented and, despite debate over the frequency of the reported side effects, they have been noticed on a large enough scale to cause alarm amongst the general public (Sue, Sue and Sue, 1994; Picton, 1997). Side-effects include:

- Sleep disturbances – insomnia, nightmares etc.
- Depression or sadness particularly with large doses and commonly when the effects of the drug begin to wear off, also on withdrawal.
- Toxic psychosis, psychotic episodes and drug dependence syndrome (Internet 3).

- Headache.
- Abdominal pain, nausea and vomiting (Novartis, 1999).
- Suppression of appetite leading to loss of weight.
- Elevated blood pressure.
- Rash, pruritis, urticaria, fever, arthralgia and scalp hair loss.
- Cardiac abnormalities (Dr Venter, 1996) including tachycardia, palpitations and arrhythmia (Novartis, 1999).
- Suppression of growth with continued use of high doses.

(Barkley, McMurray, and Edelbrock, 1990; The Merck Manual, 1997).

2.3 EVENING PRIMROSE OIL AND GAMMA LINOLENIC ACID

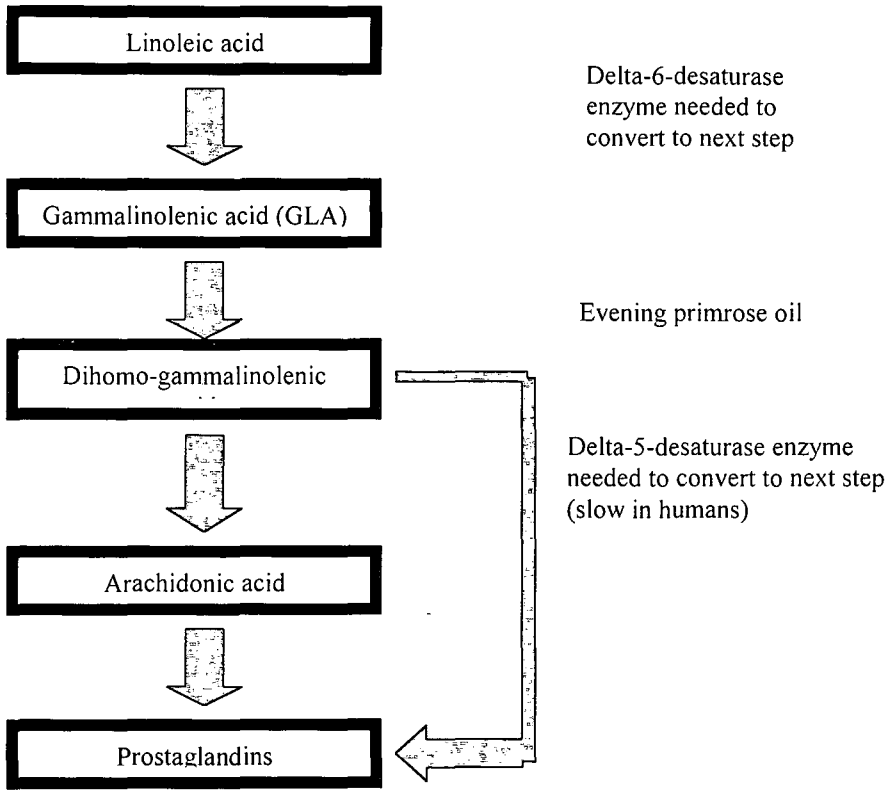
2.3.1 HISTORY

Evening primrose oil is a vegetable oil, which is, extracted from the seed of the Evening primrose plant (*Oenethiris biennis),* which is native to North America. The plant gets its name from the light yellow flowers that open at dusk (Chevallier, 1996). Research done in the 1970's revealed that the oil from the seeds was actually rich in an essential fatty acid GLA. GLA is found in all cell membranes where it controls permeability and is essential to the formation of prostaglandins in the body (Internet 3).

Prostaglandins are a range of chemical messenger substances vital to the healthy functioning of the human body. In a person with a healthy metabolism *cis*-linoleic acid can be converted into GLA however various factors can block this pathway. *Cis*-linoleic acid is a fatty acid abundant in most leafy vegetables and seeds including Evening primrose unlike GLA, which is found in very few foods (Graham, J., 1993; Ody, 1996).

FIGURE 2.1

Essential fatty acid metabolism



(Graham J., 1993)

2.3.2.1 GLA DEFICIENCIES

Due to the correspondence between the symptoms of ADD/ ADDH and GLA deficiency many researchers have theorised that the diagnosis of ADD/ ADDH may really be due to a deficiency of Gamma-linolenic acid for a variety of reasons.

Studies on animals maintained on a fat free diet showed that the animals developed a fatal condition characterised by poor growth, poor wound healing and dermatitis (Zubay, 1998). No deliberate experimentation has occurred in humans to induce this type of deficiency however cases of accidental deprivation do exist. When baby milk formulas were first developed no EFA's were added and the babies fed in this way soon developed atopic skin conditions, which were dry, scaly and eczema like. Similarly when intravenous solutions were developed for total parenteral nutrition the EFA's were omitted, patients again developed the typical atopic like symptoms, in both cases symptoms cleared up once EFA's were included in the formulas (Graham J., 1993).

It is important to remember that a simple deficiency of Essential Fatty Acid's (EFA's) due to intake is unlikely, studies have shown that in many cases the child diagnosed with ADD/ ADDH has siblings who are not affected yet they adhere to the same basic diet. There are three postulated reasons given for this deficiency:

1. ADD / ADDH children could have an inherent intestinal problem which leads to difficulty with absorption of EFA's. A large-scale

survey by the New York Institute for Childhood Development found that these children may be incapable of absorbing carbohydrates normally, therefore a problem with fat absorption would not be unlikely (Medical Hypothesis, 1981).

2. ADD/ ADDH children could have a metabolic requirement for higher levels of EFA's than normal due to a genetic difference (Medical Hypothesis, 1981; Graham J., 1993). Researchers have shown that boys have a higher requirement for GLA which coincides with a higher rate of ADD/ADHD in boys than girls.

3. ADD/ ADDH children may have a defect in their metabolism of EFA's. This is substantiated by the fact that most EFA in our diets comes in the form of cis-linoleic acid. This is then converted by enzymes into Gamma-linolenic acid and then into dihomolinolenic acid (DGLA) before it is converted into Prostaglandin E1 (PGE1), which is the usable form (Galli and Simopoulos, 1989). The initial step of this sequence is catalysed by the hormone delta-6-desaturase, which is most susceptible to blockade. This enzyme only matures after birth and therefore may lead to different rates of maturation in children (Medical Hypothesis, 1981; Graham J., 1993). Delta -6-desaturase is blocked by a number of factors including

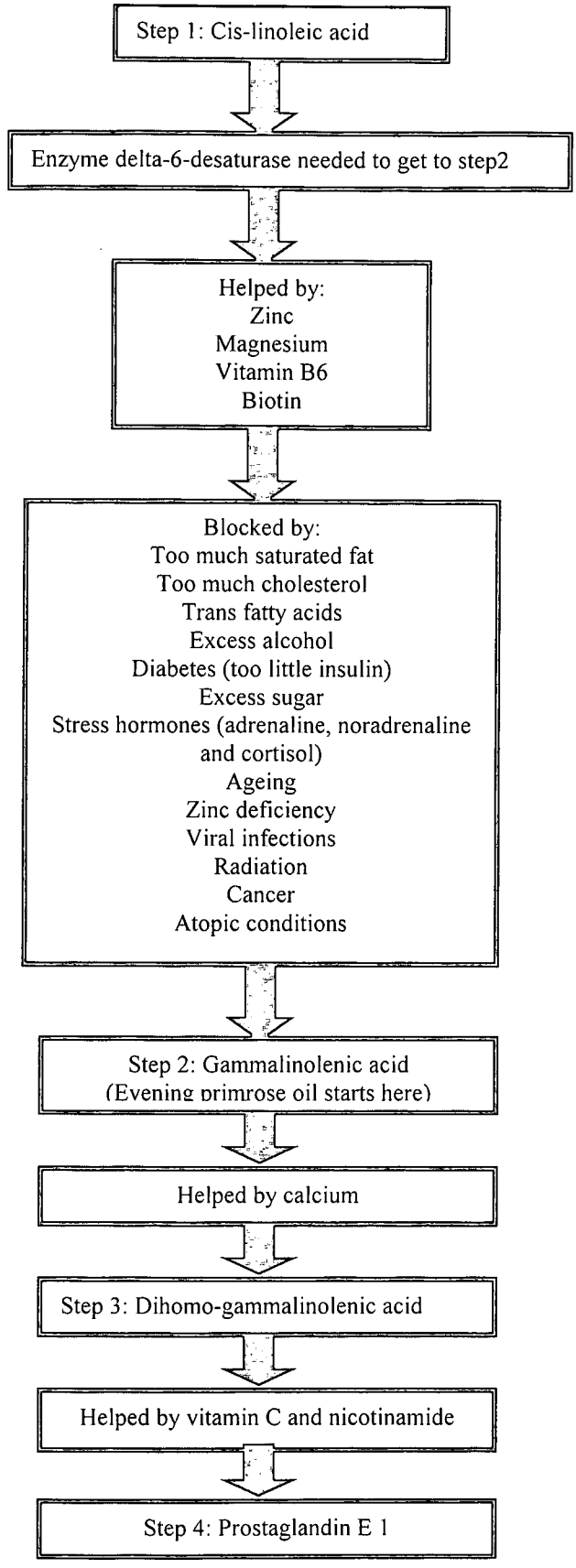
- Trans fatty acids which are commonly found in junk foods and margarine

amongst others.

- Deficiencies of zinc, magnesium and pyridoxine (vitamin B6) which are necessary for the conversion of cis-linoleic acid to GLA.

GLA is rapidly converted into DGLA. Researchers have found that children who are switched from breastmilk to formula milk often develop a form of atopic eczema, which is relieved with GLA supplementation. Breastmilk is known to contain large amounts of DGLA that can be replaced with an equivalent amount of 1g of Evening Primrose oil daily (Medical Hypothesis, 1981; Graham J., 1993).

FIGURE 2.2 THE METABOLIC CONVERSION OF CIS-LINOLEIC ACID



(Graham J., 1993)

There are a number of symptoms found in GLA deficiency, which occur also in those diagnosed with ADD/ ADDH:

- Great thirst despite normal intake of fluids (Medical Hypothesis, 1981;Graham J., 1993).
- A greater requirement for EFA's by boys than girls mirrors a similar preponderance with ADD/ ADDH where male incidence is three times greater than in females (Graham J., 1993).
- Many food additives and natural salicylates as described in the Feingold diet are only weak inhibitors of the conversion of EFA's to PGE1 and therefore their effect should only be noticeable if the levels of EFA in the body are below the normal requirement (Graham J., 1993).
- Associated illnesses like allergies, hayfever, asthma and eczema (Edwards and Bouchier, 1993; Graham J., 1993)
- Many ADD/ ADDH kids are highly sensitive to wheat and milk that aggravate their condition. It is the gluten in wheat and alpha-casein of milk, which when digested breaks down into opiod like substances. These can reduce PGE1 conversion especially if EFA levels are low (Holford, 1997; Graham J., 1993).

2.3.2.2 A POSSIBLE LINK BETWEEN DEFICIENCY OF PGE1 AND STIMULATION OF CANNABINOID RECEPTORS.

Scientists studying the mechanism of action of delta-9-tetrahydrocannabinol (THC) discovered that it attaches to its own specific receptor in the brain, the receptor has its

own unique chemical structure and the mechanism of action is distinct from that of other sedatives and psychedelics. The scientists discovered that THC binds to a specific cannabinoid receptor and mimics the effects of endogenous cannabinoids. Until recently nobody had isolated the endogenous cannabinoids. The cannabinoid receptors are amongst the most abundant in the brain, they are estimated to be between 10 and 20 times more abundant than the opiod receptors, there levels are believed to approach or exceed those for the amino acid glutamine and gamma-aminobutyric acid (GABA) (Julien, 2001).

Since THC was first isolated scientists had always believed that it acted through a pharmacologically distinct set of receptors. No one had isolated these receptors. In 1986 Howlett and co-workers showed that THC inhibits adenylate cyclase, an intracellular enzyme, and that this process requires the presence of a G-protein complex similar to that found on opiod receptors (Howlett, Qualy and Khachatrian, 1986). Recently researchers isolated the receptor and showed that THC does not directly inhibit adenylate cyclase, rather by acting on this receptor it sets off a chain of events that cumulate in the inhibition of the enzyme (Julien, 2001).

The receptors are found on the presynaptic nerve terminals, when activated they inhibit the release of other neurotransmitters from the terminals. Now that the receptor had been isolated scientists had to discover the naturally occurring ligand that would bind to the receptor and discover what its function in the body was. Devane and co-workers isolated a derivative of arachidonic acid, named anandamide, which bound to the cannabinoid

receptors and produced pharmacologically similar effects to those of the cannabinoids. Subsequent studies have confirmed that anandamide produces behavioural, hypothermic and analgesic effects similar to those of psychotropic cannabinoids. As a result of these studies scientists have decided that anandamide exhibits the essential criteria required to be classified as the endogenous ligand at cannabinoid receptors (Julien, 2001).

In 1999 it was verified that the action of anandamide on the hippocampal cannabinoid receptors was reducing neuronal excitability by inhibiting excitatory neurotransmissions at a presynaptic site. Both anandamide and THC have been shown to be only partial agonists of these receptors, THC activates only 20% of the receptors while anandamide activates 50%, it is definitely a more potent agonist and as such it requires far lower levels to produce its effects (Ameri, Wilhelm and Simmet, 1999).

Anandamide is synthesised within the neurons by a condensation reaction between arachidonic acid and ethanolamine – calcium ions and cyclic adenosine monophosphate regulate this process. The inhibition of the presynaptic release of the excitatory neurotransmitter glutamate through an inhibitory G-protein has been shown, this would account for the detrimental effects seen in marijuana use where cognitive functioning and neuronal excitability are reduced.

The major sites of action of anandamide are the hippocampus, cerebral cortex, cerebellum and basal ganglia. Effects on these areas would include:

- Distortion of time.

- Decreased ability to concentrate.
- Disruption of memory and memory storage.

These are all symptoms of the disorder known as ADD/ ADHD (Julien, 2001).

PGE1 has an inhibitory effect on the conversion of Arachidonic acid to its free form (figure 2.3) (Graham, J., 1993). Perhaps if PGE1 is deficient it may lead to an increase in the formation of anandamide. This possibility as well as the link between ADD/ ADHD and anandamide has not as yet been studied, it is entirely feasible that some form of link does exist. What levels of anandamide are needed to produce its effect on concentration and behaviour is unknown but due to the preponderance of receptors and the high affinity of anandamide it is entirely likely that low levels would produce these effects.

2.3.3 THE BASIC PRINCIPLE OF GLA THERAPY

There are a number of factors, which influence why GLA may become deficient in the body. These all rely on the conversion of *Cis*-linoleic acid into GLA, if GLA is supplied directly to the body then these factors become irrelevant. The use of potentised GLA in a low homoeopathic dilution as a means to increasing GLA levels in the body has never been performed before. The homoeopathic preparation of GLA was made to the 6CH, meaning the sixth dilution at a ratio of one part to one hundred for six successive dilutions. Although this remedy has never being used before the theory behind its prescription was derived from the approach taken by the Homoeopharmaceutical Company Heel. Homotoxicological treatment of deficiencies works on the rational that substances which are deficient in the body can be replaced by potentised dilutions of

theses same substances. It is accepted that in this form the medications are not acting on a physical level as the dilutions are too low to have any possible benefit as supplements, rather once they are potentised they become active on an energetic level, this stimulates the body's own abilities to correct the deficiency of the substance it is exposed to (Biotherapeutic Index, 2000).

Their research has shown that low dilutions of enzymes, co-enzymes and minerals can correct deficiencies seen on a physiological level. Vitamin B12 – Injeel® is a medication designed for use in vitamin B12 deficiency states. Research on this remedy showed that while supplementing with vitamin B12 in injection form did increase levels of this vitamin in the body, subsequent injections showed a growing decline in effect. The results were obtained by analysing the reticulocyte count found in the haematogram of subjects (Biotherapeutic Index, 2000). They theorised that the decline was due to a desensitisation of the organism to vitamin B12. In testing the homoeopathically diluted form of vitamin B12 they found that the levels of reticulocytes were also raised although this occurred mainly after the second and fourth injection. However these levels continued to rise after subsequent injections therefore overcoming the desensitisation found with normal vitamin B12. After comparing the results obtained from the two groups they deduced that homoeopathic medicaments and homoeopathically adjusted allopathic remedies are not subjected to the law of mass action. Instead they serve to resensitise the body to its normal content of substances found in physiological concentrations. They also deduced that the homoeopathic medication or adjusted allopathic remedy had an enhancing effect on the body's mode of reaction

(Biotherapeutic Index, 2000).

Similarly the use of minerals in low homoeopathic dilutions have been shown to correct deficiencies of the corresponding minerals in their physiological concentrations (Gilbert, 1989).

The theory behind the use of Schussler tissue salts has been around since the late 19th century when Dr Wilhelm Schussler first suggested the use of low dilutions of minerals to correct deficiencies in the organism (Gilbert, 1989). Ferrum Phosphoricum, or tissue salt number six as it is commonly known, is commonly used to treat deficiencies of Iron in the body. The concentration of minerals in tissue salts is a standard, the medications are diluted in six successive stages at a ratio of one part in ten, at each level of dilution the remedies are succussed. It is this process which is believed to make them more active. This approach is not limited to Iron deficiencies but is also applied to deficiencies of Calcium, Magnesium and Sodium Chloride. Homoeopaths around the world use these methods as fundamentals when treating basic deficiencies in the human body (Gilbert, 1989).

Both of these methods work on the rationale that the actual medicines do not work on a physical level as the physical concentrations of the deficient compounds or chemicals are too low to be able to correct a deficiency, rather the method by which they are prepared, i.e. dilution and succussion, activates the substances on an energetic level. It is on this level which they stimulate the human body allowing it to correct the deficiencies using its own natural systems. The principle behind these methods originated from the psychiatrist Rudolph Arndt (1835-1900) and pharmacologist Hugo Schultz (1853-1932), together

they formed the Arndt-Schultz principle which states that

- weak stimuli stimulate the life functions
- moderately strong stimuli accelerate them
- strong stimuli inhibit them
- the strongest stimuli suspend the life functions (Biotherapeutic Index, 2000).

2.4 GLA AND ADD/ ADHD

Since the early eighties, when a GLA deficiency was first postulated as a possible cause or factor in ADHD, much research has been done on the part of Scotia pharmaceuticals who manufacture a popular Evening primrose oil supplement, Efamol®. The research was conducted mainly in collaboration with the Hyperactive Children Support Group in the United Kingdom. The therapeutic affects of GLA supplementation had already been proven in many other disorders like Rheumatoid arthritis, eczema, high cholesterol, premenstrual syndrome and multiple sclerosis. Due to the extensive nature of the research many recommendations can now be made with regard to dosage as well as additional vitamin and mineral supplementation (Graham, 1993).

2.5 GLA ABSORPTION

Although many other seed oils contain GLA, some in higher concentrations than Evening primrose oil, research has established that for unknown reasons the Evening primrose oil was the most successful at correcting GLA deficiencies (Galli and Simopoulos, 1989). Numerous tests were performed, some using animal experiments, to show that not only did Evening primrose oil contain a relatively high percentage of GLA, it was also the

most successful at increasing the physiological concentrations of GLA and PGE1. The following tables are a summary of the results obtained from these experiments.

TABLE 2.1

Table showing the breakdown of major fatty acids present in various GLA containing oils, amounts as percentages of total fatty acid content of each oil (Galli and Simopoulos, 1989)

	PRIMROSE	FUNGAL	BORAGE	BLACKCURRANT
SATURATES	7.3	27.1	15.5	7.4
OLEIC	9	40.4	15.8	11.6
LINOLEIC	72.6	10.4	39.1	43.9
GLA	9.1	18.9	18.7	18.7

TABLE 2.2

Table showing the effects of different oils at doses which provide the same daily intake of GLA on the outflow of EFA metabolites of GLA from the mesenteric vascular bed. The results shown are the mean outflow per 30 minutes in the effluent from 6 animals in micrograms (Galli and Simopoulos, 1989).

Group	GLA	DGLA	Arachidonic	Adrenic
Borage	16.2	4.2	32.4	1.5
Blackcurrant	26.1	3.7	28.6	0.9
Fungal	12.2	3.6	15.6	0.6
Primrose	19.8	8.6	40.6	5.4

The studies that provided the above results were all randomised double blind, placebo-controlled studies (Galli and Simopoulos, 1989). As can be seen from these results, Evening primrose oil was the most successful at raising the levels of GLA metabolites.

TABLE 2.3

Table showing the effects of different oils at doses providing the same daily intake of GLA on the outflow of prostaglandin metabolites from the mesenteric vascular bed. Results are shown as the mean concentration of prostaglandins/ ml seen in the results from 6 animals (Galli and Simopoulos, 1989).

Group	PGE1	PGE2	PGI2	TxA2
Borage	2	315	4811	46
Blackcurrant	7	281	4885	129
Fungal	39	652	3043	28
Primrose	82	784	4812	26

2.6 PROSTAGLANDINS

Prostaglandins, which were first discovered in the 1930's by Ulf von Euler, were initially thought to be produced by the prostate gland. They are a collection of hormone like substances that act in very low concentrations. The prostaglandins and their related compounds - prostacyclins, thromboxanes and leukotrienes – are collectively known as eicosanoids because they all share a C-20 (twenty carbon) structure (Greek: *eikosi*,

twenty) and are all derived from arachidonic acid (Hardie, 1991). Unlike hormones they tend to act locally and are not transported by the blood stream to their site of action (Voet, Voet and Pratt, 1999). This effect is known as autocrine stimulation. Eicosanoids often work as antagonistic pairs as is the case with thromboxane A2 and prostacyclin, thromboxane A2 is released by platelets and triggers platelet aggregation. The effect is countered by prostacyclin which is released by endothelial cells, which line the blood vessels, making them unsuitable for clotting (Hardie, 1991).

Prostaglandin release is often triggered by hormones, they then modulate the effect of the hormone on the target tissue. Prostaglandins have low water solubility as they are derived from polyunsaturated fatty acids like arachidonic acid. These polyunsaturated acids are not wholly synthesised by the body but are created through the elongation and desaturation of EFA's, which are obtained from the diet (Hardie, 1991). A study in 1929 by Burr and Burr confirmed for the first time that linoleic acid is an EFA for animals (Zubay, 1998).

Eicosanoids are not stored in the cells in appreciable amounts and thus their availability is determined by their rate of synthesis and thus availability of essential fatty acids in the diet. Not only do the eicosanoids rely on polyunsaturated fatty acids for their manufacture but also on the enzymes, which are necessary for their conversion. One example of such an enzyme is cyclo-oxygenase. This enzyme is inhibited by the familiar drug aspirin which accounts for most of the numerous effects and side effects of this drug (Hardie, 1991).

3.4 THE FUNCTIONS OF PROSTAGLANDINS IN THE BODY

Prostaglandins are known to be involved in the production of pain and fever, regulation of blood pressure, blood coagulation and reproduction and are thought to act on mood and memory (Voet, Voet and Pratt, 1999). GLA is a precursor of one type of prostaglandin, prostaglandin E1 (PGE1). It is PGE1 together with the fluidising effects of GLA, which is responsible for the many varied therapeutic effects of Evening primrose oil.

The Swedish scientist, Von Euler, first discovered prostaglandins in the 1930's. He isolated them from the seminal fluid and deduced that they came from the prostate gland, hence the name. Although he was correct in his assumption he didn't realise that many different tissue types throughout the body in fact produce them. Prostaglandins are in fact cell regulators, which control the second to second functions of every cell and organ in the body. Unlike hormones they don't have a general effect on the body but rather act locally with a short duration of action. Prostaglandins are removed from the blood during a single passage through the lungs, part of the reason for their short life span is their natural instability as well as their highly efficient mechanisms for breakdown (Zubay, 1998).

They have so far been isolated from blood vessel walls, macrophages, platelets, duodenal secretions, nerves and every organ in the body. Their main functions are believed to be as messengers, which regulate the activity of the tissues in which they are produced as well as regulators of certain key enzymes (Hardie, 1991. So far 3 main series of prostaglandins have been isolated: PG1, PG2, and PG3. Each of these has a unique chemical structure

and within each series different types exist, each is classified by a different letters A, B, C, D, E, F etc. The three series are each derived from a different base fatty acid). Series 1 and 2 both come from the linoleic acid family. Series 3 comes from eicosapentanoic acid a member of the alpha-linolenic acid family, which is most commonly found in oily seafood's (Zubay, 1998).

Health problems begin when the different series of prostaglandins are out of balance with one another. The balance between 1 and 2 series prostaglandins is often influenced by diet. In inflammatory conditions the end products of arachidonic acid metabolism – prostaglandins series 2, cyclo-oxygenase and thromboxane A2 – are found in abundance whereas PGE1 is not being produced in sufficient quantities (Graham J., 1993). For most inflammatory conditions like arthritis, the medication used (non-steroidal anti-inflammatory drugs – NSAID's) work by inhibiting the formation of prostaglandins from fatty acids. The trouble with this approach is that all prostaglandin formation is disrupted including the good ones. Evening primrose oil has a balancing function in that it restores normal levels of the anti-inflammatory PGE1 and so it manipulates the prostaglandin balance in a different way (Graham J., 1993; Voet, Voet and Pratt, 1999).

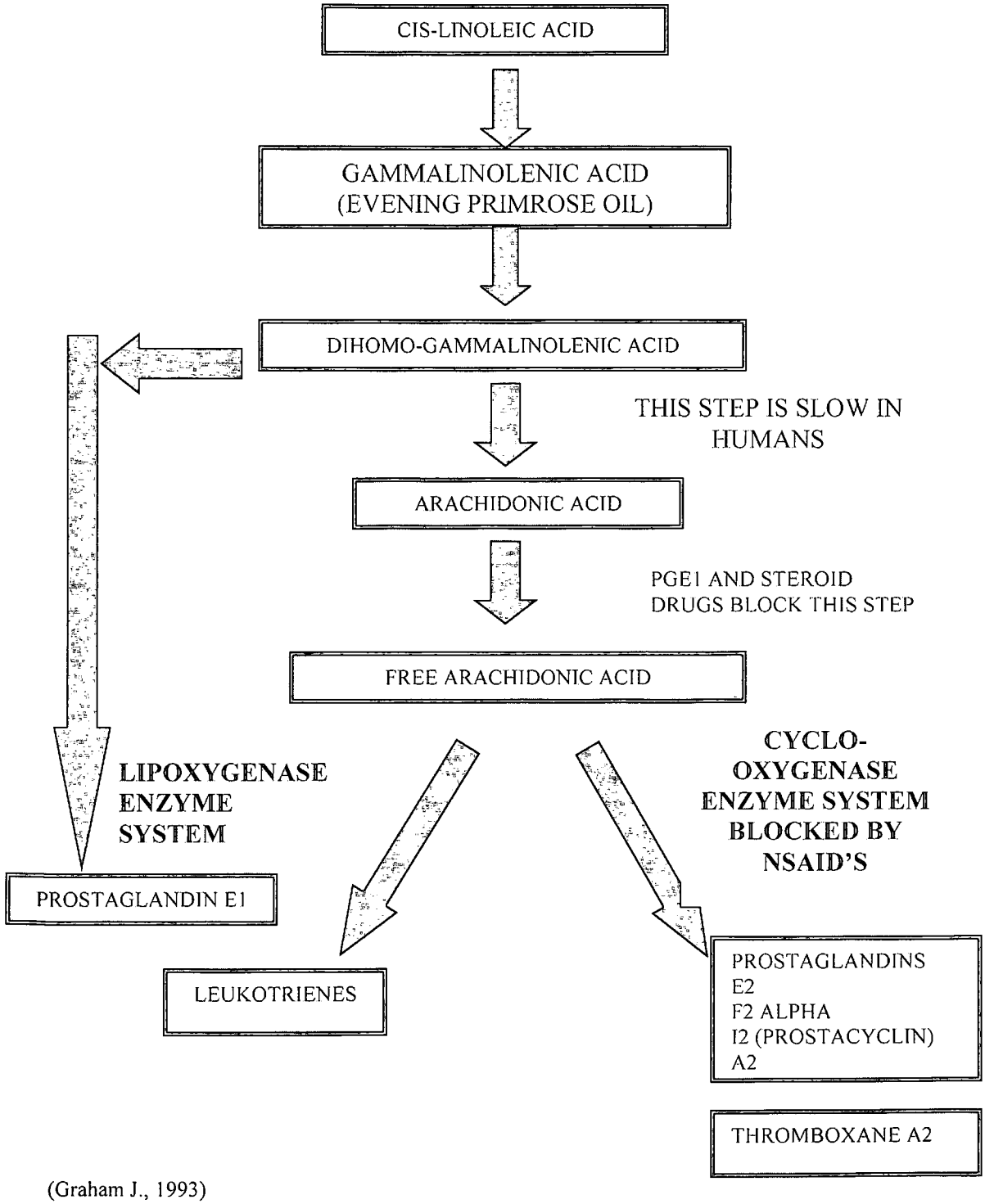
PGE1 functions in the body:

- Promotes vasodilation.
- Lowers arterial pressure.
- Inhibits cholesterol synthesis.
- Inhibits platelet aggregation.

- Elevates cyclic Adenosine Monophosphate (Cyclic-AMP)
- Inhibits inflammation and arthritis.
- Inhibits the synthesis of pro-inflammatory substances.
- Inhibits the release of lysosomal enzymes, which are believed to cause damage during the inflammatory response.
- Inhibits abnormal cell proliferation.
- Influences behaviour.
- Affects nerve conduction.
- Regulates the release and post-synaptic functions of neurotransmitters.
- Has insulin like actions and can increase the potential of insulin in the body.

(Graham J., 1993; Zubay, 1998).

FIGURE 2.3
PROSTAGLANDIN SYNTHESIS FROM THE LINOLEIC ACID FAMILY



(Graham J., 1993)

2.8 PLACEBO

In homoeopathic practice this is a non-medicated substance which is relatively inert pharmacodynamically. The medicine can be used to contrast the effects of relative non-medication in controlled experiments with that of medication in two or more groups of patients of comparable composition (Gaier, 1991). Experimentation has shown that no substance is entirely inert whether it has been potentised or not. Therefore, the placebo is referred to as relatively inert. For consistency the placebo in this research was impregnated in the same manner with the same percentage of alcohol as the homoeopathically potentised GLA.

2.9 SUMMARY

ADD/ ADHD is a common problem amongst children from the age of five years on, conservative estimates put it at 5% of schoolage children (DuPaul *et al.*, 1998). Current medical treatment favours the use Methylphenidate hydrochloride (Ritalin®), a psychostimulant medication that can have severe side-effects (Merk Manual, 1992). Many parents are opting to try natural approaches like supplementation or Homoeopathy to avoid the side effects associated with drugs like Ritalin.

Although there are many approaches to try very few have been scientifically proven and as such parents are unsure which treatments to use and often resort to experimenting themselves.

CHAPTER 3

3. MATERIALS AND METHODS

3.1 STUDY DESIGN

This was a clinical trial in which two experimental groups were compared with a placebo control group, the object was to determine whether Evening primrose oil and/ or GLA in a homoeopathic dilution could be used as alternative treatments for ADD/ ADHD. The thirty participants were randomly divided into three groups of ten prior to the study:

- Group one was the treatment group receiving Evening primrose oil.
- Group two was the treatment group receiving a homoeopathic preparation of potentised GLA.
- Group three was the control group receiving a placebo, which was virtually identical to the homoeopathic preparation in group two but unmedicated.

During the interviews with the prospective participants it was explained that the three groups were randomly allocated prior to the study, as such there was a one in three chance of the subject being placed on placebo medication. It was also explained that following the study these participants would be given the option of trying the two treatments at no cost to the participant.

3.2 ADVERTISING AND RECRUITMENT PROCEDURE

Adverts were placed in all the local papers for the Durban area advertising a study on the alternative treatment of children with ADD/ ADHD (Appendix H). Posters were placed at

strategic points in local pharmacies and libraries and pamphlets outlining the details of the study were also available at these points (Appendix H).

3.3 SELECTION CRITERIA

Interested parents who called in response to the advert were briefed on the details of the study. Those who were interested were assessed according to the following criteria:

Inclusion criteria

- Only boys were used in this study
- Participants had to be between the ages of 6 and 13 years old.
- Participants had to have been previously diagnosed by a medical professional as having ADD or ADHD.

Exclusion criteria

- Any child with a history of seizures or epilepsy was excluded from the study as Evening primrose oil is contra-indicated in this condition.
- Children who where at that time taking chronic medication like anti-depressants and cortisone were excluded from the study.
- Children who were currently taking Ritalin or any other medication for ADD/ ADHD had to go off the medication for a period of one week before commencing the study and for the duration of the study. Those who could not abstain from their current medication were excluded from the study.

Subjects who conformed to all the above parameters were provided with detailed information on the study and allowed to ask questions with regards to the study. When both child and parent agreed to participate the child was given an informed assent form (Appendix D) which again outlined the details of the study in simple words for the child's understanding. Once they accepted this they were asked to sign the form signaling their agreement with the rules of the study. Parents were also given an informed consent form to sign (Appendix C). The directions for each of the three possible medications was explained at this stage and again when the patient received their allocated medication from the dispensary.

3.4 SAMPLE GROUP

The sample group that was initially chosen for this research was set at 60. It was initially thought that this would be the minimum number necessary to provide a good representation of children diagnosed with the disorder and to provide statistically significant results. After 6 months of canvassing for participants it was decided to reduce this number to a total of 30. The following were the reasons given for the planned decrease in the sample group:

- Many interested participants expressed reservations about having to cease their current treatment regimes.
- Many schools were not interested in giving their approval as they felt that even a study of one month could affect a child's overall performance and thus their ability to progress to the next grade. They were also concerned that the child's

behaviour over the course of the study could become a distraction to fellow class mates and thus decrease the general class performance.

- A number of the participants in the study dropped out after 2-3 weeks as the parents felt that their children were making no progress and their hyperactive behaviour was becoming intolerable.
- Some participants had to be eliminated from the study after parents were unable to comply with the treatment regime of three doses per day at regular intervals.

The decrease in the sample group was proposed by the researcher and after consultation with the statistician it was approved by the Durban Institute of Technology (DIT) Faculty of Health Sciences Research Committee.

The sample group was randomly chosen from participants who responded to various forms of advertising in the highway area. The newspapers that were selected are distributed in areas with varied income and racial preponderance, no attempt was made to focus on any particular racial group. The demographics of ADD/ADHD have until now shown that the disorder is found equally in all races but that the reported cases are often restricted to middle and higher income groups or groups with access to medical and educational services (Picton, 1997). In the final group 24 of the participants were Caucasian, 5 were Asian and 1 was African.

Reasons for this racial breakdown include the following:

- Obtaining a clinical assessment diagnosing a child as having ADD/ADHD is a time consuming and relatively expensive procedure.

- Not all parents have the time to monitor their child's progress, particularly lower income groups where the parents may both be working all day.
- Many lower income families are not aware or educated on issues like ADD/ADHD and so parents are more likely to think they have a troublesome child than a child with a learning disability. Also the schools which these children attend are sometimes lacking in basic facilities like a school psychologist who could usually identify learning disorders as they present.

3.5 RANDOMISATION

Dr David Naude (Department of Homoeopathy, Durban Institute of Technology) conducted the randomisation of this study in a double blind manner. Prior to the study commencing the numbers of patients were randomly allocated to one of the three groups. The labels on the medications for groups two and three were simply stated with a group number and the directions for taking the remedy. Once the patient was accepted into the study they were taken through to the clinic reception where the researcher then left them to receive their medicines. The clinic secretaries or the dispenser on duty dispensed the medicines as assigned to that patient number on the randomisation list. The Evening primrose oil being unavoidably visually distinguishable from the placebo and homoeopathic GLA- necessitated the absence of the researcher at all times when medicines were dispensed. Patients were also informed not to discuss the type of medication they received on all subsequent consultations with the researcher.

3.6 INTERVENTION

Group 1 received Evening primrose oil in a capsule form. Pharma Natura supplied the evening primrose oil from their Vitaforce range. Each capsule consisted of 500mg of Evening primrose oil in a gel capsule, the percentage of GLA per capsule was 10%, and therefore 50mg of GLA was provided per capsule. The batch number of the stock used was 530480 with an expiry date of 03/2004. Each participant in this group had to take one capsule three times daily.

Group 2 received homoeopathically prepared GLA 6CH in pillule form. The pure GLA that was used in the preparation of the remedy was supplied by Nu-Check (USA), this company specialises in plant extracts and oils. The GLA was provided with a purity guarantee (Appendix I) which states that the substance provided was prepared as chromatographically pure with a purity of greater than 99%. A trituration of the GLA was made by hand using Method 6 of the German Homoeopathic Pharmacopoeia (GHP) (Appendix J). The centesimal scale of dilution was used and the vehicle for dilution was lactose powder. The trituration was carried up to the third level of dilution. At this point the trituration was converted into a liquid preparation using Method 8a of the GHP (Appendix J). The fourth stage of dilution used purified water as the dilution vehicle, the fifth stage used 30% ethanol as the dilution vehicle while the sixth and final stage used 70% ethanol as the dilution vehicle (GHP, 1991). Pillules, supplied by Pharma Natura, were then medicated with the 6CH GLA in liquid form using the triple impregnation method. Pillules were supplied to the participant in number 8 size glass vials. Each participant in this group had to take three pillules sublingually three times daily.

Group 3 received Placebo in pillule form (i.e. neutral pillules). The pillules were prepared in the same manner as those in group2 using the triple impregnation method using non-medicated 70% ethanol. Pillules were supplied to the participant in number 8 size glass vials. Each participant had to take three pillules sublingually three times daily.

Both groups 2 and 3 were prepared in a room filtered by a laminar airflow apparatus. All attempts were made to maintain a sterile environment throughout the preparation process.

As the patients were being treated and evaluated at home the researcher relied upon the honesty and integrity of the guardians to ensure that they complied with all instructions. The guardians were given an information letter at the onset of the study and once the consent forms were signed the specific instructions for the evaluation and treatment of the children was explained to the guardian. Only once they were sure of their responsibilities were they taken to the clinic dispensary to receive their respective medicines. All participants were contacted on a weekly basis to enquire about compliance and any difficulties they may have been experiencing, any who had been unable to conform were rejected from the study and their results excluded.

3.7 MEASUREMENT TECHNIQUES

3.7.1 THE ADHD RATING SCALE- IV

The ADHD Rating Scale – IV (Appendix A and B) was developed by G. J. DuPaul, T. J. Power, A. D. Anastopoulos and R. Reid in 1998. It was developed for use by clinicians

and doctors in research as well as with regards to individual patient assessment. It is based on the DSM –IV criteria (Appendix H) for ADD/ ADHD with questions targeting both the inattention and hyperactivity / impulsivity aspects. Every odd question is aimed at the inattention aspect and every even question is aimed at the hyperactivity / impulsivity. The responses used reflect the frequency of the behaviour so that a question can be answered as being never or rarely, sometimes, often or very often. Due to the distinction between the two different components of the disorder the scale can be used to assess improvement in either one of these areas or as a total score. Each component consists of nine symptoms each. The final scores can also be compared to the normative data for children of similar age groups based on studies in the United States of America (Appendix B) (DuPaul *et al.*, 1998). For the purpose of this research only the mean scores of each category and the total were used for analysis.

There are at present many different behaviour based questionnaires in use for the assessment of ADD/ ADHD, unfortunately very few of these are directed at the DSM-IV criteria which are the standard set for diagnosis of this disorder. The questions asked in the questionnaire are adaptations of the DSM-IV criteria with the difference being that the questions omit the word *"often"*, instead respondents are asked to indicate the frequency with which each symptom is noted. By alternating the questions regarding the two components of the disorder, the developers aimed to reduce response bias (DuPaul *et al.*, 1998). The scale consists of two versions, a school and a home version. The home version was used for the purpose of this study as the researcher felt that it would be easier to gain the parent's co-operation than the teachers.

The questionnaires (Appendix A) were handed to the parents at the initial interview where it was explained to the parent how to use the questionnaire. Parents were asked to read through the questionnaire to ensure that they understood all of the questions. The questionnaires were to be completed on a weekly basis with one prior to the study reflecting the child's normal behaviour and thereafter one every week of the study to reflect the child's progress while undergoing treatment. The total number of questionnaires completed was five per patient with a minimum of two consultations. Parents were asked to ensure that the completion of the questionnaires was always done by the same person and not by different parents as this would have an influence on the reliability of the data collected. Where possible the initial questionnaire was filled out at the first consultation, however in some situations only one parent was present and so it was decided that the questionnaire would be completed at home where both parents would provide input. A follow-up consultation was held at the completion of each participant's five weeks where children and parents were given an opportunity to raise any questions.

3.8 DATA ANALYSIS

3.8.1 STATISTICAL METHODS

This study comprised of subjective data only, the score of symptoms from the ADHD Rating Scale. This score of symptoms was subdivided into three further variables of inattention, hyperactivity and a total score, being the sum of the first two variables. Five sets of readings were taken for each subject.

Due to the relatively small sample size (n=30) non-parametric tests were applied to the three variables for analysis.

3.8.2 STATISTICAL ANALYSIS

The data was analysed in terms of an intra-group comparison first and secondly an inter-group comparison. For the intra-group comparison Friedman's T test for repeated measures was employed. If the null hypothesis was rejected a multiple comparison procedure for use with Friedman's T test would be used to specify the week in which maximum improvement occurred.

The inter-group comparison used the Kruskal-Wallis H test to compare the three groups. If the null hypothesis was rejected the Dunn-procedure would be applied to determine which group differed from the rest.

With the exception of Dunn's procedure, all statistical analyses were carried out using the computer software program SPSS version 9. Dunn's procedure was performed manually using the equation in Procedure 2 below.

PROCEDURE 1 – FRIEDMAN'S T TEST

Friedman's T test was used for intra-group comparisons to determine whether there were significant improvements within each of the groups with respect to the three different variables.

I. Hypothesis testing

The null hypothesis H_0 states that there is no difference between the groups at the α=0.05 level of significance. The alternative hypothesis H_1 states that there is a difference between the visits.

II. Decision rule

At the α=0.05 level of significance, the null hypothesis is rejected if $p < \alpha$ where p is the observed level of significance. Otherwise, the null hypothesis is accepted at the same level of significance.

If the null hypothesis is rejected for the Friedman's F test, then multiple comparison procedures will be performed to determine which week differed from the rest.

PROCEDURE 2 – KRUSKAL-WALLIS H TEST

The Kruskal-Wallis H test was used for inter-group comparisons to determine whether a difference existed at any of the evaluations between the two experimental groups and the control group.

I. Hypothesis testing

The null hypothesis H_0 states that there is no difference between the groups at the α=0.05 level of significance. The alternative hypothesis states H_1, states that there is a difference between the groups.

II. Decision rule

At the α=0.05 level of significance, the null hypothesis is rejected if $p < \alpha$ where p is the observed level of significance. Otherwise, the null hypothesis is accepted at the same level of significance.

If the null hypothesis is rejected for the Kruskal-Wallis H test, then multiple comparison procedures will be performed to determine which group differed from the rest.

PROCEDURE 3 – DUNN PROCEDURE

The Dunn procedure, also known as the Bonferroni t Test (Howell, 1987), is a multiple comparison procedure. If the null hypothesis H_0 was rejected for Friedman's T test or the Kruskal-Wallis H test, then the Dunn procedure was performed in order to identify which of the evaluations were different.

Method

If R_i and $R_{j'}$ are the i^{th} and j'^{th} treatment rank totals, then we declare then we declare R_i and $R_{j'}$ significantly different if

$$|Ri - Rj| \geq z\sqrt{\frac{bk(k+1}{6}}$$

Where:

z = a value in the standard normal probabilities table corresponding to

$$1 - [\alpha/k\ (k\text{-}1)]$$

α = experimentwise error rate

k = the number of questionnaires filled out

b = the number of blocks (i.e. the total number of patients in the group)

(Daniel, 1978)

3.9 ETHICAL CONSIDERATIONS

Due to the nature of the research a placebo group had to be included as a control for the other two groups. As the volunteers for each group were randomly allocated there was a possibility that anyone of the participants could have been administered placebo medication. Participants were briefed on this at the onset of the study. It was explained to them about the need for placebo, they were also informed that should they be given the placebo medication they would be told about this at the completion of the study and be given the option of trying the other two treatments at no cost to themselves. Both parties i.e. the guardians and participants were made to sign a consent form and assent form to signify their understanding of this and their agreement to participate despite the possibility of receiving placebo medication.

CHAPTER 4

4. RESULTS

4.1 INTRODUCTION

This chapter details the results obtained from the statistical analysis of the data collected from the three groups in the study using the ADHD Rating Scale IV (Appendix A).

4.2 ADMISSIBILITY OF THE DATA

Only the data collected from the research was accepted for use in this chapter. The data used for the analysis was collected in the manner discussed in Chapter 3

4.3 RAW DATA

Refer to appendices for the raw data relating to the results.

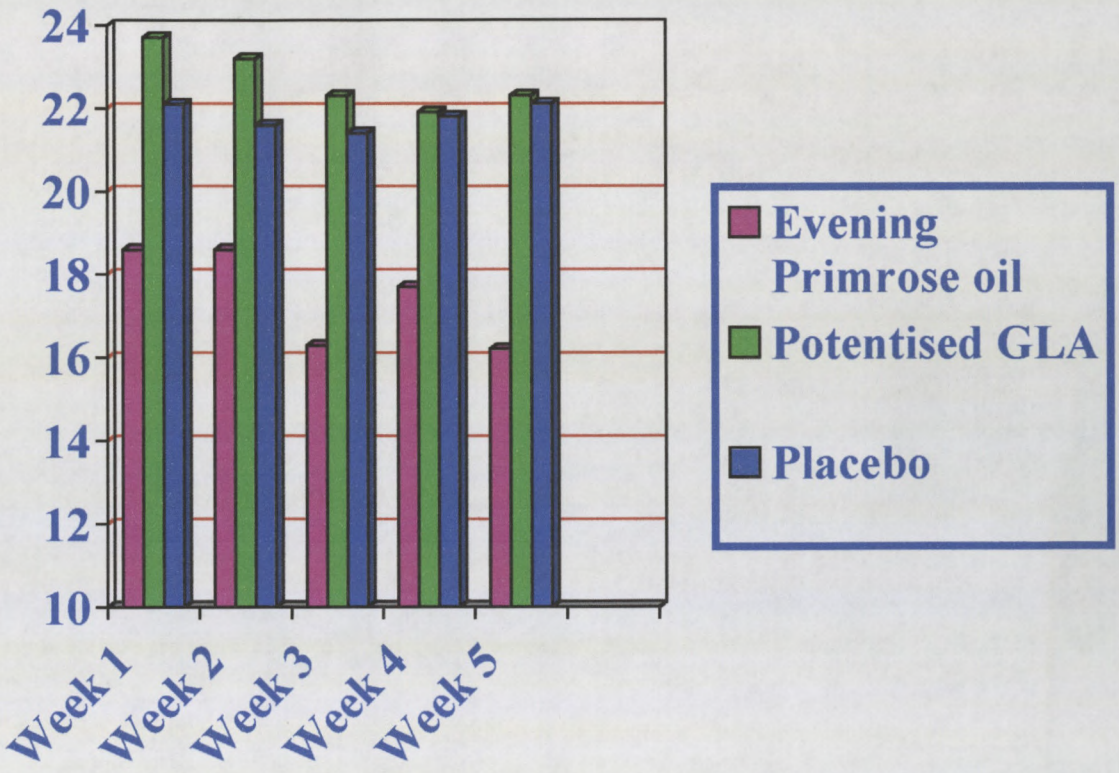
The lower the number of points scored in each test, the more positive the results were, and vice versa. Each test was divided into three categories:

- Score for inattention.
- Score for hyperactivity and impulsivity
- Combined score for the above two categories

The results reflect the mean of the actual scores obtained and not percentages.

4.4 BARCHARTS OF THE MEAN SCORE

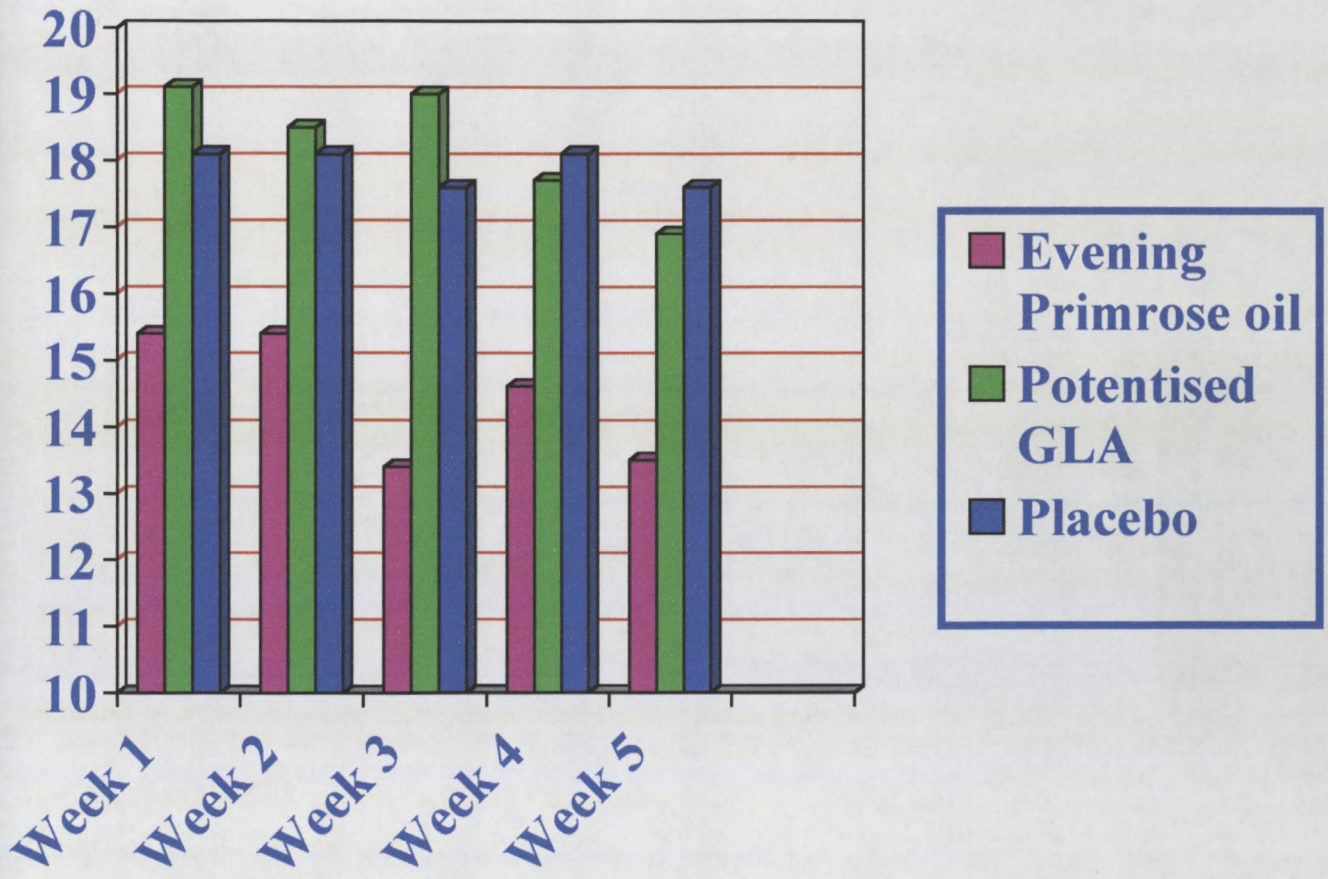
Figure 4.1
Barchart comparing the mean Inattention scores of all 3 groups



Week one is the baseline or initial evaluation made prior to commencement of treatment.

Figure 4.2

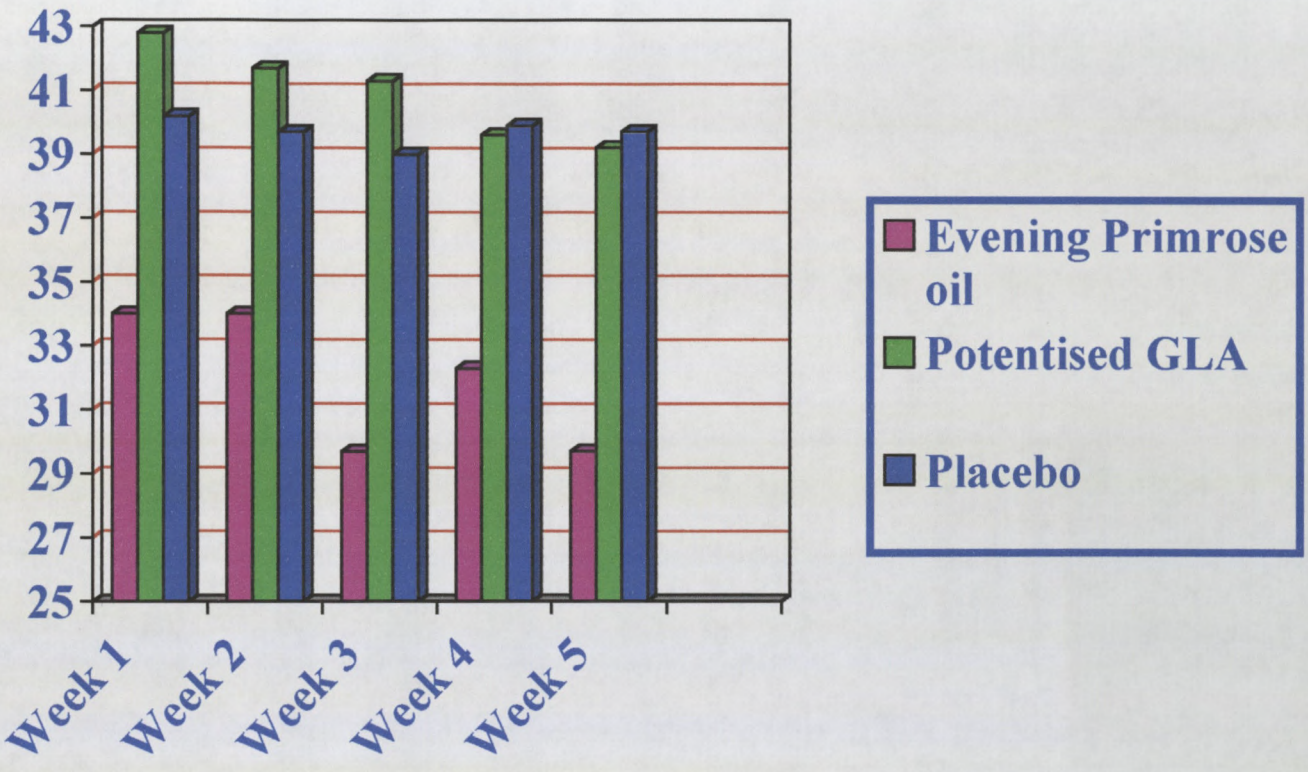
Barchart comparing the mean Hyperactivity and Impulsivity scores of all 3 groups



Week one is the baseline or initial evaluation made prior to commencement of treatment.

Figure 4.3

Barchart comparing the mean Total scores of all 3 groups



Week one is the baseline or initial evaluation made prior to commencement of treatment.

4.5 PROCEDURE 1 – FRIEDMANS F TEST

4.5.1 INTRA GROUP COMPARISON OF THE DATA FOR GROUP 1 – EVENING PRIMROSE OIL

Table 4.1

SCORES	P- VALUE	CONCLUSION
INATTENTION	.323	NO DIFFERENCE
HYPERACTIVITY AND IMPULSIVITY	.440	NO DIFFERENCE
TOTAL	.277	NO DIFFERENCE

At the $\alpha = 0.05$ level of significance, the test revealed that there was no statistically significant difference for the inattention, hyperactivity and impulsivity or the total scores ($p > 0.05$ – the null hypothesis H_0 is accepted).

4.5.2 INTRA GROUP COMPARISON OF THE DATA FOR GROUP 2 – HOMOEOPATHICALLY POTENTISED GLA

Table 4.2

SCORES	P – VALUE	CONCLUSION
INATTENTION	.323	NO DIFFERENCE
HYPERACTIVITY AND IMPULSIVITY	.440	NO DIFFERENCE
TOTAL	.277	NO DIFFERENCE

At the $\alpha = 0.05$ level of significance, the test revealed that there was no statistically significant difference for the inattention, hyperactivity and impulsivity or the total scores ($p > 0.05$ – the null hypothesis H_0 is accepted).

4.5.3 INTRA GROUP COMPARISON OF THE DATA FOR GROUP 3 - PLACEBO

Table 4.3

SCORES	P - VALUE	CONCLUSION
INATTENTION	.323	NO DIFFERENCE
HYPERACTIVITY AND IMPULSIVITY	.440	NO DIFFERENCE
TOTAL	.277	NO DIFFERENCE

At the $\alpha = 0.05$ level of significance, the test revealed that there was no statistically significant difference for the inattention, hyperactivity and impulsivity or the total scores ($p > 0.05$ – the null hypothesis H_0 is accepted).

4.6 PROCEDURES 2 AND 3 – KRUSKAL-WALLIS H TEST AND THE DUNN PROCEDURE

4.6.1 INTER GROUP COMPARISONS OF THE DIFFERENT SCORES FOR GROUPS 1, 2 AND 3

Table 4.4

SCORES	P – VALUE				
	QUEST. 1	QUEST. 2	QUEST. 3	QUEST. 4	QUEST.5
IA	.049*	.176	.019*	.087	.013*
HI	.309	.544	.215	.453	.414
TOT	.105	.247	.037*	.181	.072

* Denotes significant difference

IA = Inattention

HI = Hyperactivity and Impulsivity

TOT = Total combined score

At the $\alpha = 0.05$ level of significance the test revealed that there was a statistically significant difference for the Inattention scores on questionnaires 1, 3 and 5 and for the

Total scores on questionnaire 3 ($p < 0.05$ – the null hypothesis H_0 is rejected). Therefore the Dunn procedure was applied to establish which of the groups were different.

At the $\alpha = 0.05$ level of significance, there was no statistically significant difference for; the Inattention scores on questionnaire's 2 and 4; the Hyperactivity scores on all three questionnaires; the Total combined scores for questionnaires 1,2,4 and 5 ($p > 0.05$ – the null hypothesis H_0 is accepted).

4.6.1.1 THE DUNN PROCEDURE

Table 4.5

		RANK TOTALS
INATTENTION FOR QUESTIONNAIRE 1	EVENING PRIMROSE OIL	18.6
	POTENTISED GLA	23.7
	PLACEBO	22.1
INATTENTION FOR QUESTIONNAIRE 3	EVENING PRIMROSE OIL	16.3
	POTENTISED GLA	22.3
	PLACEBO	21.4
INATTENTION FOR QUESTIONNAIRE 5	EVENING PRIMROSE OIL	16.2
	POTENTISED GLA	22.3
	PLACEBO	22.1
TOTAL FOR QUESTIONNAIRE 3	EVENING PRIMROSE OIL	29.7
	POTENTISED GLA	39.2
	PLACEBO	39.7

EQUATION: If $|Ri - Rj| \geq z\sqrt{\frac{bk(k+1)}{6}}$ then R_i and R_j are declared significantly different.

If $\alpha = 0.15$, $k = 3$ and $b = 10$ then $z = 1.96$

Therefore $z\sqrt{\frac{bk(k+1)}{6}} = 1.96\sqrt{\frac{10(3)(3+1)}{6}} = 4.61$

Table 4.6

	$R_1 - R_2$	$R_1 - R_3$	$R_2 - R_3$
INATTENTION FOR QUESTIONNAIRE 1	5.1*	3.5	1.6
INATTENTION FOR QUESTIONNAIRE 3	6*	5.1*	.9
INATTENTION FOR QUESTIONNAIRE 5	6.1*	5.9*	.2
TOTAL FOR QUESTIONNAIRE 3	9.5*	10*	.5

* denotes a significant difference

4.7 CONCLUSION

Using the inter group comparison a significant difference was detected in the inattention scores for questionnaire 1 (p=0.049), using Dunn's procedure it was determined that a statistically significant difference existed between groups 1 and 2 for the inattention scores on questionnaire 1.

Using the inter group comparison a significant difference was detected in the inattention scores for questionnaire 3 (p=0.019), using Dunn's procedure it was determined that a

statistically significant difference existed between groups 1 and 2 and groups 1 and 3 for the inattention scores on questionnaire 3.

Using the inter group comparison a significant difference was detected in the inattention scores for questionnaire 5 ($p=0.013$), using Dunn's procedure it was determined that a statistically significant difference existed between groups 1 and 2 and groups 1 and 3 for the inattention scores on questionnaire 5.

Using the inter group comparison a significant difference was detected in the total scores for questionnaire 3 ($p=0.037$), using Dunn's procedure it was determined that a statistically significant difference existed between groups 1 and 2 and groups 1 and 3 for the total scores on questionnaire 3.

CHAPTER 5

5. DISCUSSION

The conventional medical treatment of ADD/ ADHD is the prescribed use of cerebral stimulant medication like Methylphenidate hydrochloride. Drug trials and research into the effectiveness of stimulant medication has produced varying results. Most researchers agree that these medications produce a slight to dramatic improvement in the behavioural symptoms displayed by children with ADD/ ADHD, these symptoms however are only one component of the disorder (Zillmer and Spiers, 2001). The inattention component of the disorder is often unaffected or responds poorly to such medication, so while a child may become more manageable in the classroom environment the problem of a learning disability remains.

Stimulant medication has some severe limitations: side effects which are common and range from appetite suppression to severe personality changes; the effects of stimulant medication are of a short duration (often only 4 hours), thus the child is required to receive frequent dosing; there is often a rebound effect or worsening of core symptoms as the medication wears off (this usually happens towards the end of day when the parent and child are together and thus it can negatively effect their relationship with one another); children often resist compliance with the medication (children are aware of the side effects produced and this can influence their actions, others dislike the medication simply for the taste which they describe as bitter); the medications have a limited effect on learning disabilities and inattention; these medications do not cure as the core symptoms are seen to reemerge as the medication wears off (Sue, Sue and Sue, 1994; Zillmer and Spiers, 2001).

As a result of these limitations many parents have chosen to find other alternatives. Psychological counseling with behavioural interventions is one of the more successful approaches however it too has limitations. Many parents do not have the finances to pay for this type of treatment and often the resources are not easily available (particularly in rural areas). Research has shown that while behavioural interventions are often extremely successful their success tends to be restricted to the context for which they were developed (for example improvement in impulse control in the classroom brought about by behavioural intervention may not extend to the home environment unless new measures are developed for this specific context) (Sue, Sue and Sue, 1994). Schools, which cater for children with learning disabilities, often employ these behavioural interventions, the problem is that these schools are in short supply and often have waiting lists of three or more years. These behavioural management programs are of the most benefit to the younger children, after the age of ten children show a natural resistance to external structuring and control which negates the effectiveness of these programs. Educators and parents agree that while behavioural intervention can be successful it requires close supervision and support from the psychologist who developed it (Zillmer and Spiers, 2001).

Other alternatives like supplementation and Homoeopathy are not new, however the amount of exposure they receive and the research into their effectivity is minimal when compared with mainstream treatments like Ritalin®. The first research into the use of Evening Primrose oil as a supplement for "hyperactivity" was performed in 1980 by Scotia Pharmaceuticals using their brand product Efamol®. Initial results were

encouraging and over the years the company has developed recommendations on dosage as well as combinations which increase the effectiveness of GLA supplementation. Most of the research has taken place in the United Kingdom and USA, very little coverage has appeared in South Africa. Although literature on this research does exist it is not easily accessible, during the course of this research project the researcher was able to find only three references to the studies performed by Scotia Pharmaceuticals. The first two references are articles from the early eighties documenting the initial studies, which were performed using Efamol® in co-operation with the Hyperactive Children's Support Group in the UK. The third reference was in a book entitled Evening Primrose oil by Graham, J. (1993), this book is not widely kept in South Africa and a copy was only obtained once the study had already commenced. The Efamol® website has been inoperative for the last two years and other online references were related to other products produced by Scotia Pharmaceuticals.

The use of homoeopathically prepared GLA has never been seen before, while it is deemed safe its effectivity is unknown. The reason for administering the GLA in homoeopathically prepared form was derived from the methods used by the Heel company and the Schussler approach of restoring biochemical tissue salts. Both of these methods make use of diluted levels of chemicals or compounds prepared in a homoeopathic manner in order to correct deficiencies in the body. The rationale behind these approaches is that simple dilutions of chemicals or compounds do not have the necessary concentration to correct the deficiencies, therefore the remedies that were prepared in a homoeopathic manner using succussion were not acting on a physical level

but on an energetic level which stimulates the body's innate abilities to correct these deficiencies.

The researcher chose to use boys for the research for two principle reasons, firstly boys seem to be more affected by the disorder with statistics showing a prevalence in the region of 4:1 over girls (Picton, 1997), secondly it is accepted that boys have a higher need for GLA (Graham, J., 1993) and thus would be more likely to display a deficiency of this fatty acid. This chapter attempts to explain the results of the statistical analysis on the efficacy of Evening primrose oil supplementation and the use of homoeopathically prepared GLA.

Statistical analysis

The measurement of the difference between the treatment groups and the placebo group for the baseline showed a statistically significant difference ($p=0.049$) in the inattention score of the Evening primrose oil group (group 1) and the Homoeopathically prepared GLA (group 2). Usually this difference would signify an inappropriate measure of comparison, however this disorder has two components that are being measured, inattention and hyperactivity/ impulsivity. No statistically significant difference was noted for the hyperactivity/impulsivity component nor was there a statistically significant difference for the total score in the baseline measurement. As has been discussed previously children with ADD/ ADHD may be predominantly inattentive, predominantly hyperactive/ impulsive or of a combination of the two. The difference that has been noted between the two treatment groups in the baseline signifies that group 1 contained more children of the predominantly inattentive type.

Analysis of the data from the ADHD Rating Scale IV

Friedmann's F test was used to perform an intragroup comparison for each of the groups on the five questionnaires that were completed. No statistically significant difference was noted for either of the groups. A simple comparison of the mean totals for each component of the questionnaire showed that the Evening primrose oil group (group 1) and the Homoeopathically prepared GLA group (group 2) showed a reduction in all three components over the five questionnaires. The placebo group (group 3) showed no improvement only fluctuations with the last questionnaire having almost the same mean totals as the first questionnaire.

The Kruskal-Wallis H test was used for the intergroup comparisons over each of the five weeks. A statistically significant difference ($p=0.049$) was found in the first questionnaire between groups 1 and 2 as discussed above. A further significant difference was noted between groups 1, 2 and 3 for the inattention scores in questionnaires 3 ($p=0.013$) and 5 ($p=0.013$) for the inattention scores and the Total score in week 3 ($p=0.037$). These differences were analysed using Dunn's Procedure where it was found that an improvement in the Evening Primrose oil group (Group 1) was responsible for the difference noted.

Limitations of the study

The ADHD Rating Scale IV was used to subjectively assess the severity of the inattention and hyperactivity/impulsivity symptoms seen in the participants. The symptoms that are

rated in the questionnaire can be influenced by external factors, which are separate from the child's condition.: work load at school varies from week to week, this can lead to fluctuation in the child's behaviour and performance; the parents mood and attitude can be influenced by work load and relationships, these factors can influence the way in which they perceive their child's behaviour and so influence the scores they give to the child's symptoms.

Children who were accepted into the study had to have been previously diagnosed by a medical practitioner. As has been pointed out previously not all medical practitioners take the time to analyse and assess the child sufficiently before diagnosing ADD/ ADHD. Due to budget constraints children could not be referred for individual psychological assessment. For this reason some of the children who were entered into the study may well have been misdiagnosed. ADD/ ADHD is a dynamic disorder with many different factors influencing a child's behaviour. Psychological intervention may be necessary in those children whose problems stem from psychosomatic factors like relationships. Supplementation and treatment with homoeopathically potentised GLA cannot claim to replace effective psychological interventions but merely help to correct deficiencies. The fact that an improvement was noted in the treatment groups signifies that further research is necessary to establish the exact role such interventions may play in the treatment of ADD/ ADHD. When the study was first proposed it was intended to have a sample size of sixty and therefore a group size of twenty. Although many parents volunteered their children for the research, there were relatively few who were willing or able to cease their child's current treatment. In some situations parents felt that they would be risking their

child's progress at school whilst others were influenced by the schools that refused to co-operate should the children be taken off their medication (Ritalin®).

The relatively short period of assessment is a result of these same factors, schools were not willing to risk disruption to normal school routine for a longer period. Certainly a longer assessment period of two to four months would have given a more accurate reflection of a child's progress in terms of a new treatment.

CHAPTER 6

6. CONCLUSIONS AND RECOMMENDATIONS

6.1 CONCLUSIONS

The aim of this study was to determine and compare the relative efficacy of supplementation using Evening primrose oil and homoeopathically potentised GLA, in the management of ADD/ ADHD. Using the ADHD-IV Rating Scale, participants were assessed on a weekly basis to determine what, if any, progress was made. Intra group comparisons of each of the groups showed that there was no statistically significant improvement with in the individual scores. However it was apparent that there was a downward trend or improvement with regards to the mean scores of the Evening primrose oil group, to a lesser extent this was seen in the Potentised GLA group, this indicates there was some slight improvement in the participants of these two groups. The Placebo group showed an increase in mean scores and therefore no progress whatsoever. The inter group comparisons showed a statistically significant difference in a number of areas.

The first difference that was noted was between groups one and two on the inattention scores of questionnaire one. This difference may be explained by the fact that the mean scores at the initial presentation of symptoms was significantly lower in the Evening Primrose oil group as compared to the Potentised GLA group. This difference was marked again on the third questionnaire where the Evening primrose oil group differed from both of the other groups signifying a progressive improvement. The same significant difference was noted on the fifth questionnaire for the inattention component.

In the intergroup comparison of total scores a significant improvement was shown in the Evening primrose oil group over the other two groups. As a result it can be stated that Evening primrose oil was effective as an intervention as it managed to significantly improve the inattention scores. Although the homoeopathically prepared GLA did not show any statistically significant improvement it was clear that there was a slight improvement in the inattention scores, as such further research should be done to establish if a longer treatment period and a higher potency might show more significant improvement.

The fact that an improvement was noted in the treatment groups signifies that further research is necessary to establish the exact role such interventions may play in the treatment of ADD/ADHD. Recommendations could then be made with regard to optimal dosage and period of supplementation.

6.2 RECOMMENDATIONS

There are a number of recommendations which can be made with regard to future studies on this or related topics:

- If the effect of GLA is being researched it may be useful to limit participants to those that already suffer with some form of atopic disorder like asthma, hayfever and atopic eczema. Although children with no atopic problems did respond to the therapy the improvement in atopic symptoms would provide more data for analysis and perhaps more conclusive results

- Treatments should be compared to a combined group of Evening primrose oil and potentised GLA as this may lead to increased absorption of the GLA. A similar method is used in calcium supplementation where calcium tissue salts are taken simultaneously with the mineral supplement (Gilbert, 1989).
- Higher potencies of the homoeopathically prepared GLA should be tested to establish differences like frequency of dosage. Higher potencies like a 30CH or 200CH often require less frequent dosage and so a reduction of frequency from three times daily to twice or once daily might be optimal (Gaier, 1991).
- The dose of the Evening primrose oil should be elevated to a level of 3 grams per day as current research has shown this to be more successful (Graham J., 1993). This source of information only became available after the study had already commenced and so it was too late to alter the dosage. Current research also shows that a combination of evening primrose oil with a omega 3 containing oil like cod liver oil significantly increases the progress, the ratio that is recommended here is 4:1 (evening primrose: cod liver) (Graham J., 1993).
- The interaction between different minerals and vitamins and the conversion of GLA into prostaglandins should be noted, as such a good supplement containing the essentials of these would be advisable. This may help to increase the benefit of GLA supplementation.
- The research should be conducted over a longer period like three to six months as some of the patients in the treatment groups reported ongoing progress after the 4 weeks of treatment.

- Further study needs to be done on the possible link between ADD/ADHD and the endogenous cannabinoid, anandamide. If a link is discovered an antagonist of anandamide could have significant benefits to the future treatment and research of ADD/ADHD.

Using the same principle of this research the treatment could be applied to different conditions like those suffering with atopic conditions, arthritis or menopause to establish what success these conditions would show to the same treatment. There are an abundance of people who suffer from these conditions and as such it would be easier to get volunteers particularly for longer studies.

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APPENDIX A

ADHD RATING SCALE-IV: HOME VERSION

Child's name _____. **Age** _____. **Grade** _____.
Completed by: **Mother** _____. **Father** _____. **Guardian** _____. **Grandparent** _____.

Circle the number that *best describes* your child's behavior over the past week.

	Never or rarely	Sometimes	Often	Very often
1. Fails to give close attention to details or makes careless mistakes in schoolwork.	0	1	2	3
2. Fidgets with hands or feet or squirms in seat.	0	1	2	3
3. Has difficulty sustaining attention in tasks or play activities.	0	1	2	3
4. Leaves seat in classroom or in other situations in which remaining seated is expected.	0	1	2	3
5. Does not seem to listen when spoken to directly.	0	1	2	3
6. Runs about or climbs excessively in situations in which it is inappropriate.	0	1	2	3
7. Does not follow through on instructions and fails to finish work.	0	1	2	3
8. Has difficulty playing or engaging in leisure activities quietly.	0	1	2	3
9. Has difficulty organizing tasks and activities.	0	1	2	3
10. Is "on the go" or acts as if "driven by a motor".	0	1	2	3
11. Avoids tasks (e.g., schoolwork or homework) that require sustained mental effort.	0	1	2	3
12. Talks excessively.	0	1	2	3
13. Loses things necessary for tasks or activities.	0	1	2	3
14. Blurts out answers before questions have been completed.	0	1	2	3
15. Is easily distracted.	0	1	2	3
16. Has difficulty awaiting turn.	0	1	2	3
17. Is forgetful in daily activities.	0	1	2	3
18. Interrupts or intrudes on others.	0	1	2	3

(DuPaul, 1998.)

APPENDIX B

ADHD RATING SCALE –IV: HOME VERSION
SCORING SHEET FOR BOYS

Child's name _____. **Date** _____. **Age** _____.

%ile	HI 5-7	HI 8-10	HI 11-13	HI 14-18	IA 5-7	IA 8-10	IA 11-13	IA 14-18	Total 5-7	Total 8-10	Total 11-13	Total 14-18	%ile
99+	26	25	25	19	24	26	27	25	43	49	51	41	99+
99	25	24	24	18	23	25	26	24	42	48	50	40	99
98	22	21	21	16	20	22	24	23	40	42	47	36	98
97	21	18	18	16	20	19	22	16	37	37	38	32	97
96	19	17	18	15	18	18	21	18	36	34	37	30	96
95	17	17	18	13	16	17	20	17	34	31	35	28	95
94	17	15	18	12	15	16	19	16	33	29	34	27	94
93	17	15	16	11	15	15	18	15	30	27	34	27	93
92	16	14	16	11	14	15	18	14	30	26	33	26	92
91	16	14	15	11	13	14	18	14	29	26	32	25	91
90	15	13	14	10	13	14	18	14	29	25	31	23	90
89	14	13	13	10	12	14	17	13	28	24	30	21	89
88	14	12	12	10	12	13	17	12	27	24	30	21	88
87	13	11	11	9	12	13	16	12	25	23	28	20	87
86	13	11	10	9	12	12	16	11	22	23	26	20	86
85	12	10	10	8	11	12	14	11	22	22	23	19	85
84	12	10	9	8	11	12	14	10	21	21	22	18	84
80	11	9	8	7	9	11	10	9	19	20	19	16	80
75	9	8	7	6	8	9	9	8	18	17	14	13	75
50	5	4	3	2	5	6	5	4	10	10	7	7	50
25	3	2	1	0	2	3	2	1	6	5	4	3	25
10	1	0	0	0	0	0	1	0	2	1	1	0	10

(DuPaul, 1998.)

APPENDIX C

INFORMED CONSENT FORM

TITLE OF RESEARCH PROJECT:

A placebo-controlled study of the relative efficacy of Evening Primrose oil supplementation or Gamma-linolenic acid in low Homoeopathic potency, in the management of Attention Deficit Disorder with or without Hyperactivity of schoolgoing boys.

NAME OF SUPERVISOR:

Dr Ashley Ross M.Tech (Hom)(TN) B.Mus (UCT).

NAME OF RESEARCH STUDENT:

Justin B. Middleborough.

DATE: _____

PLEASE CIRCLE THE APPROPRIATE ANSWERS:

1. Have you read the research information sheet? Yes / No
2. Have you had the opportunity to asks questions regarding this study? Yes / No
3. Have you received satisfactory answers to your questions? Yes / No
4. Have you received enough information about this study? Yes / No
5. Do you agree not to discuss any of the particulars of your child's treatment with any other study participants you may come into contact with for the duration of the study? Yes/ No
6. Who have you spoken to with regards to this study?
   _____.
7. Do you fully understand the implications of your child's involvement in this study? Yes / No
8. Do you understand that you are free to withdraw from this study? Yes / No
   1. At any time
   2. Without having to give a reason for withdrawing, and
   3. Without affecting your future health care.
9. Do you agree to voluntarily participate in this study? Yes / no

If you have answered no to any of the above, please obtain the information before signing

I_____hereby give consent for my child to be involved in the above mentioned research project.

Patient /Subject Name: _____.
(In block letters)

Guardian / Parent Name:_____. Signature
(In block letters)

Witness Name:_____. Signature
(In block letters)

Research Student Name: Justin B. Middleborough. Signature

APPENDIX D

Informed assent form.

Dear patient,

This letter has been designed to give you an understanding of the study in which you may become a patient if you agree to the conditions explained here. By signing this form you will be giving me, the researcher, permission to involve you in my study. This means that you will be asked to take treatment for your condition, Attention Deficit Disorder, which you may know as Hyperactivity.

If you agree you will be given one of three different treatments, all of these may make you feel better but they may also cause a return of your old problem, you may feel restless and unable to sit still and think about one thing for a long time. None of the treatments will cause any bad things to happen to you and you can decide to stop taking the treatments at any time you decide to.

The reason for this study is to determine whether there is another way to treat the disorder known as Attention Deficit Disorder. This is where people are unable to think about one thing for a long time or to sit still for a long time to listen to one person talking. During this study children like you will be given treatment for Hyperactivity. The study will last for one month and during this time you are asked to please not tell any of your friends what kind of treatment you are getting, it has to be a secret until the study is finished. Your parents will fill in a questionnaire every week answering questions about you and your behaviour. Please remember you cannot pass or fail this so you don't have to try and behave differently, just be yourself.

APPENDIX D

The three treatments are as follows:

- **Evening primrose oil – this is plant oil that given in a soft jelly like pill.**
- **Potentised Homoeopathic Gamma Linolenic Acid – this is a special medicine that given in a sugar pill that tastes sweet.**
- **Placebo treatment – this is also given in a sugar pill that tastes sweet but doesn't contain any medicine.**

If you are given the Placebo treatment, the one that doesn't contain any medicine, you can choose to get one of the other treatments for free after the study is over.
If you would like to take part in this study you can write your name on the bottom of this form or make a fingerprint.

Patient's Name:_____

Parent's Name:_____

Researcher's Name:_____

Date:_____

APPENDIX E

Letter to the principal/ teacher

To whom it may concern,

Please be informed that _____ , grade _____ and class _____ , will be participating in a research study run by Technikon Natal. The title of this research study is

"The relative efficacy of Evening Primrose oil and low Homoeopathic potency Gamma Linolenic acid in the management of Attention Deficit Hyperactivity Disorder (ADHD)."

During this study participants have been asked to stop taking their current medication for ADD/ ADHD. They will instead be taking one of three proposed medications.

- Potentised Homoeopathic Gamma Linolenic acid which comes in the form of white sugar granules taken under the tongue.
- Evening Primrose oil capsules, which are swallowed.
- Placebo, which is indistinguishable from the Homoeopathic medicine but, is not medicated.

There are no side effects from these medications but the child may show a return to old symptoms of ADD/ ADHD. You are asked to please bear this in mind over the next month as the research extends for a one-month period. The parents of the child will be filling out a questionnaire weekly until the duration of the study to evaluate their child's symptoms. Should you have any queries or objections to this study or if you feel this study may negatively impact on the child's performance and thus progress to the next grade, you are asked to not hesitate and contact either the parent, researcher or supervisor whose details appear below.

I would like to take this opportunity to thank you for your time and patience which may be tested in the coming month should you agree to this study.

Yours appreciatively

Justin Middleborough (Final year Homoeopathy student at Natal Technikon)

Contact details:

Researcher – Justin Middleborough	Tel 2666044 (h) cell 084 319 1568
	Tel 3041234 (w)
	Tel 2042041 (Tech.)
Supervisor – Dr Ashley Ross	Tel 2042041 (w)

APPENDIX F

GROUP 1- EVENING PRIMROSE OIL

Patient number	Questionnaire 1			Questionnaire 2			Questionnaire 3			Questionnaire 4			Questionnaire 5		
	IA	HI	Tot	IA	HI	Tot	IA	HI	Tot	IA	HI	Tot	IA	HI	Tot
1	15	16	31	18	18	36	14	17	31	15	15	30	9	10	19
2	10	10	21	12	13	25	15	19	34	15	16	31	15	16	31
3	19	16	35	14	13	27	10	8	18	10	8	18	10	8	18
4	27	27	54	27	27	54	21	21	42	27	27	54	21	25	46
5	16	12	28	17	13	30	17	10	27	21	10	31	18	9	27
6	23	20	43	21	20	41	22	21	43	20	21	41	19	20	39
7	17	7	24	24	4	28	23	3	26	23	5	28	23	3	26
8	15	12	27	9	4	13	10	5	15	10	5	15	10	6	16
9	24	14	38	26	23	49	13	11	24	18	18	36	20	17	37
10	19	20	39	18	19	37	18	19	37	18	21	39	17	21	38

IA = Inattention
HI = Hyperactivity and Impulsivity
Tot = Total combined score

APPENDIX F

GROUP 2 – POTENTISED GLA

Patient number	Questionnaire 1			Questionnaire 2			Questionnaire 3			Questionnaire 4			Questionnaire 5		
	IA	HI	Tot	IA	HI	Tot	IA	HI	Tot	IA	HI	Tot	IA	HI	Tot
1	26	21	47	23	20	43	23	17	40	21	18	39	24	16	40
2	22	18	40	20	17	37	20	18	38	21	16	37	22	17	39
3	23	23	46	23	23	46	23	23	46	23	23	46	23	23	46
4	24	11	35	23	10	33	23	10	33	22	9	31	22	10	32
5	25	21	46	27	18	45	25	19	44	25	10	35	25	6	31
6	25	25	50	26	25	51	27	27	54	27	27	54	27	27	54
7	24	22	46	24	22	46	24	23	47	24	23	47	24	23	47
8	20	15	35	20	15	35	9	9	18	9	9	18	8	8	16
9	24	15	39	22	15	37	27	23	50	25	22	47	25	20	45
10	24	20	44	24	20	44	22	21	43	22	20	42	23	19	42

IA = Inattention
HI = Hyperactivity and Impulsivity
Tot = Total combined score

APPENDIX F

GROUP 3 - PLACEBO

Patient number	Questionnaire 1			Questionnaire 2			Questionnaire 3			Questionnaire 4			Questionnaire 5		
	IA	HI	Tot	IA	HI	Tot	IA	HI	Tot	IA	HI	Tot	IA	HI	Tot
1	19	17	26	19	7	26	19	7	26	19	7	26	19	7	26
2	25	24	49	18	23	41	19	26	45	23	27	50	27	25	52
3	27	22	49	27	18	45	24	16	40	24	16	40	24	16	40
4	26	27	53	27	27	54	27	27	54	27	27	54	27	27	54
5	19	20	39	19	22	41	22	24	46	22	22	44	21	22	43
6	27	25	52	27	25	52	27	25	52	27	25	52	27	25	52
7	26	14	40	25	14	39	25	15	40	22	12	34	25	13	38
8	19	13	32	18	13	31	18	11	29	19	13	32	16	12	28
9	8	6	14	9	8	17	9	7	16	8	13	21	9	9	18
10	25	23	48	27	24	51	24	18	42	27	19	46	26	20	46

IA = Inattention
HI = Hyperactivity and Impulsivity
Tot = Total combined score

APPENDIX G

DOES YOUR CHILD SUFFER WITH

ATTENTION DEFICIT DISORDER (ADD) OR HYPERACTIVITY (ADHD)

RESEARCH WITH **FREE** TREATMENT IS BEING CARRIED OUT AT TECHNIKON NATAL HOMOEOPATHY DAY CLINIC ON BOYS AGED BETWEEN 6 AND 13 FOR MORE INFORMATION TELEPHONE 2042041

APPENDIX G

DOES YOUR CHILD SUFFER WITH

ATTENTION DEFICIT DISORDER (ADD) OR HYPERACTIVITY (ADHD).

RESEARCH WITH FREE TREATMENT FOR THESE DISORDERS IS CURRENTLY BEING CONDUCTED AT TECHNIKON NATAL HOMOEOPATHY DEPT.

GENERAL REQUIREMENTS ARE THAT VOLUNTEERS MUST BE:

- *MALE;*
- *BETWEEN THE AGES OF 6 AND 13;*
- *MUST BE IN POSSESSION OF A DOCTOR'S CERTIFICATE DIAGNOSING THEM AS HAVING ADD OR ADHD;*
- *CHILDREN MUST BE TAKEN OFF ANY OTHER FORM OF TREATMENT FOR THE DURATION OF THE RESEARCH – ONE MONTH.*

FOR MORE INFORMATION CONTACT TECHNIKON NATAL HOMOEOPATHY DAY CLINIC ON 031 204-2041

APPENDIX H

DSM-IV DIAGNOSTIC CRITERIA FOR ATTENTION DEFICIT/HYPERACTIVITY DISORDER

A. **Either (I) or (II):**

(I) **Inattention:** Six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

1. Often fails to give close attention to details or makes careless mistakes in homework, work or other activities.
2. Often has difficulty sustaining attention in tasks or play activities.
3. Often does not seem to listen when spoken to directly
4. Often does not follow through on instructions and fails to finish schoolwork, chores or duties in the workplace.
5. Often has difficulty organizing tasks or activities.
6. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort.
7. Often loses things necessary for tasks or activities.
8. Is often easily distracted by extraneous stimuli.
9. Is often forgetful of daily activities.

(II) **Hyperactivity and Impulsivity:** Six (or more) of the following symptoms Of hyperactivity- impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity.

1. Often leaves seat in classroom or in other situations where remaining seated is expected.
2. Often runs about or climbs excessively in situations in which it is inappropriate.
3. Often has difficulty playing or engaging in leisure activities quietly.
4. Often fidgets with hands or feet or squirms in seat.
5. Is often "on the go" or often acts as if "driven by a motor."
6. Often talks excessively.

Impulsivity.

7. Often blurts out answers before questions have been completed.
8. Often has difficulty awaiting turn.
9. Often interrupts or intrudes on others.

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings.

D. There must be clear evidence of clinically significant impairment in social, academic or occupational functioning.

Code based on type:

Combined type: Criteria for I and II are met for past 6 months.

Predominantly Inattentive type: Criteria for I are met but Criteria for II are not met for past 6 months.

Predominantly Hyperactive-Impulsive type: Criteria for II are met but Criteria for I are not met for past 6 months.

APPENDIX I

PURITY GUARANTEE

NU- CHEK GENERALLY PREPARES CHROMATOGRAPHICALLY PURE COMPOUNDS LISTED IN OUR CATALOG AS HAVING A PURITY GREATER THAN 99%+. VARYING DEGREES OF PURITY (I.E. RELATIVELY PURE GREATER THAN 90%) ARE ALSO LISTED. COMPOUNDS OF LESSER DEGREE PURITY CAN ALSO BE OBTAINED BY SPECIAL REQUEST.

ALL PRODUCTS MADE AVAILABLE UNDER OUR LABEL AREGUARANTEED TO MEET THE MINIMUM SPECIFICATIONS DESIGNATED AT THE TIME OF SALE. AGE OR CONDITION OF STORAGE MAY ALTER CHEMICAL PROPERTIES FOR WHICH CHANGE WE CANNOT BE HELD LIABLE.

IF AT THE TIME OF SALE ANY OF OUR PREPARATIONS ARE FOUND TO BE INFERIOR OR OF A DEGREE PURITY LESS THAN SPECIFIED, NU-CHEK WILL SUPPLY YOU (FREE OF CHARGE) AN ADEQUATE REPLACEMENT, OR AT OUR OPTION, REFUND YOUR PURCHASE PRICE. ALL CLAIMS MUST BE MADE WITHIN 60 DAYS OF INVOICE DATE. (ANTIOXIDANTS TEND TO ALTER NORMAL COMPOUND FUNCTIONS AND ARE NEVER ADDED UNLESS REQUESTED SPECIFICALLY.)

OUR UNSATURATED COMPOUNDS ARE INSERTED IN VIALS BY VOLUME AND NOT WEIGHT - FLUSHED WITH NITROGEN SEVERAL TIMES AND SEALED UNDER HIGH VACUUM. EACH VIAL CONTAINS AT LEAST THE MINIMUM AMOUNT SPECIFIED ON THE LABEL. EXACT WEIGHTS MAY BE OBTAINED IF DESIRED WITH A $2.00 RESEAL CHARGE PER VIAL.

(NU-CHECK PREP)

APPENDIX J

GERMAN HOMOEOPATHIC PHARMACOPOEIA (EXTRACT)

Method 6: Triturations

Preparations made according to Method 6 are Triturations of solid basic drug materials with lactose as the vehicle unless otherwise prescribed. Triturations made up to and including the 4th dilution are triturated by hand or machine in a ratio of 1 to 10 (decimal dilution) or 1 to 100 (centesimal dilution). Unless otherwise stated, the basic drug materials are reduced to the particle size given in the Monograph (mesh aperture). Quantities of more than 1000 g are triturated by mechanical means.

The duration and intensity of trituration should be such that the resulting particle size of the basic drug material in the first decimal or centesimal dilution is below 10μm at 80 per cent level; no drug particle should be more than 50μm.

Triturations up to and including the 4th decimal or centesimal dilution are produced at the same duration and intensity of trituration.

Trituration by hand

Divide the vehicle into three parts and triturate the first part for a short period in a porcelain mortar. Add the basic drug material and triturate for 6 minutes, scrape down for 4 minutes with a porcelain spatula, triturate for a further 6 minutes, scrape down again for 4 minutes, add the second part of the vehicle and continue as above. Finally add the third part and proceed as before. The minimum time required for the whole process will thus be 1 hour. The same method is followed for subsequent dilutions.

Method 8a: Liquid preparations made from triturations

Preparations made by Method 8a are liquid preparations produced from triturations made by Method 6.

To produce a 6 c liquid dilution, 1 part of the 4c trituration is dissolved in 99 parts of water and succussed. 1 part of this dilution is combined with 99 parts of ethanol 30 per cent to produce the 6c liquid dilution by succussion.