THE EFFECT OF SPINAL MANIPULATION IN CHRONIC LOW BACK PAIN SUFFERERS IN TERMS OF CLINICAL AND IMMUNE CELLULAR RESPONSES

by

HENDRIK THEODORUS KRUGER

A Dissertation submitted in partial compliance with the requirements
for the Masters Degree in Technology: Chiropractic,
in the Faculty of Health Services at the Technikon Natal.

I, Hendrik Theodorus Kruger,
do declare that this dissertation is representative of my own work.

APPROVED FOR FINAL SUBMISSION

Hendrik Theodorus Kruger — DATE 5/5/99

V NAICKER
SUPERVISOR
MBChB M.Med
F.F Path D.H.S.M. — DATE 13/05/99.

DEDICATION

I dedicate this dissertation to Avril, my wife,

Reinhardt and Rikus, my sons,

for their love, support and guidance.

ACKNOWLEDGEMENTS

A special word of thanks to the following people:

Dr V Naicker, my supervisor, for his guidance, advice and support.

Mr Doorasamy and his team at the Department of Haematology, University of Natal for their co-operation.

The patients who participated in this study.

Mrs Van Zyl, from the research department, and Mr Worku, the statistician at Technikon Natal for their and assistance.

My wife, for the hours she spent typing.

My family and friends.

Dr Till for his guidance and patience.

My colleagues and classmates, for inspiration and motivation.

ABSTRACT

A search of the literature failed to reveal previous studies performed to determine the effect of spinal manipulation in chronic low back pain sufferers, in terms of clinical and immune cellular responses. Previous studies have dealt with either clinical or immune cellular responses but not both in the same study. In response to this, the objective of this study was to evaluate the effect of spinal manipulative therapy in chronic mechanical low back pain patients in terms of the patients' perception, objective clinical findings as well as the cellular component of the immune system, in order to determine the influence this treatment has on these three parameters.

This study was a single, blind placebo-controlled study and consisted of experimental and descriptive design. Thirty volunteers between the ages of 18 and 50 years, who presented to the Technikon Natal Chiropractic Day Clinic complaining of chronic mechanical low back pain, were included in the study. These patients were carefully screened by means of a case history, physical examination, lumbar spine and pelvis regional examination and radiographic examination of the lumbar spine and pelvis (where clinically indicated), to detect the presence of lumbar facet syndrome, sacro-iliac syndrome or a combination of these two entities. This thorough examination also ensured that they had no contra-indications to chiropractic spinal manipulation (see literature review - Chapter 2).

The patients were randomly divided into two groups of fifteen each. The control group received placebo treatment by using the Vacotron Unit (Vacotron 436 by Enraf Nonius)

over the lumbar area and switching it on for a period of 15 minutes per session. The experimental group was treated with lumbar spine or sacro-iliac manipulation as indicated by the physical findings. Data was collected once a week, prior to the first, second and third consultation and then two weeks later at the fourth (follow-up) consultation, in order to compare pre- and post-treatment results.

A Goniometer (BROM II) was used to measure the subjects' lumbar spine ranges of motion and an Algometer ("FDK 20 Force Dial") was used to record the subjects' pain sensitivity. These were recorded by the researcher to detect the objective response of the patients. The Numerical Pain Rating Scale 101, the Short-form McGill Pain Questionnaire and the Oswestry Back Disability Index were used to record the patients' response to pain in a subjective manner. Blood samples were collected at the University of Natal Medical School by means of venipuncture in EDTA vacutainer tubes and analysed with an Epics Profile II Flow Cytometer.

The Wilcoxon's Signed Rank Test (intra-group analyses) was used to determine whether any significant changes occurred over the treatment period within each study group.

The Mann-Whitney U-Test (inter-group analyses) was used to determine whether there was any significant difference between the two groups at the time of the first and the fourth (follow-up) consultations. All confidence intervals were constructed at 95% i.e. $\alpha = 0,05$.

The results indicated that the experimental group was effective at improving certain lumbar ranges of motion and improving disability over the treatment period. Both groups showed an improvement in the quality of pain as measured by the Short-form McGill Pain Questionnaire, but there was no difference between the groups. The control group showed an improvement in the intensity of pain as measured by the Numerical Rating Scale 101 in the short term, but the trend in the longer term was for the experimental group to improve.

A statistically significant improvement in pain sensitivity in the experimental group was found at the third consultation. Although the remainder of the readings resulted in no statistically significant difference, the mean score showed a possible trend for the experimental group in clinical improvement towards the end of the treatment period.

The results of the blood and lymphocyte profiles showed a statistically significant change in the CD 4 count of the experimental group over the treatment period. However, no statistically significant changes were found for the rest of the immunophenotypes. A statistically significant difference was found between the two groups in terms of haemoglobin levels over the whole treatment period. This could be attributed to the preponderence of females in the one group.

The results of this investigation are based on a small number of patients and require confirmation or modification by using a larger sample size and more treatments. Long term trials, in which patients are monitored for a longer period are also required. This may result in the production of more significant results.

For whatever reason, this study did not demonstrate the sort of evidence that others have done in terms of the efficacy of spinal manipulation in managing low back pain. This may be a reason why there was no a significant response in the experimental group in terms of the cellular component of the immune system.

Suggestions for improved study design have been made.

TABLE OF CONTENTS

1. **CHAPTER 1 : INTRODUCTION** 1

2. **CHAPTER 2 : REVIEW OF THE RELATED LITERATURE** 5

2.1 Introduction 5

2.2 Mechanical low back pain 7

2.2.1 Incidence and prevalence of mechanical low back pain 7

2.2.2 Aetiology of low back pain 9

2.2.3 Mechanism of joint fixation 17

2.3 The efficacy and cost- effectiveness of spinal manipulative therapy 25

2.4 The immune system 29

2.4.1 Neural-immune interaction 34

2.4.2 Neural-immune interaction mediated via lymphocyte receptors 35

2.4.2.1 Neurotransmitters 35

2.4.2.1.1 Nor-epinephrine 35

2.5.2.1.2 Serotonin 37

2.5.2.1.3 Acetylcholine 38

2.5.3 Endocrine-immune interactions 39

2.5.3.1 Hormones 39

2.5.3.1.1 Prolactin and growth hormone 39

2.4.3.1.2 Adrenocorticotrophic hormone 40

2.4.3.2 Neuropeptides 42

2.4.3.2.1 Substance P 43

2.4.3.2.2 Vasoactive Intestinal Peptide 46

2.4.4 Spinal manipulation and immune function 47

3. CHAPTER 3 : MATERIALS AND METHODS 56

3.1 Introduction 56

3.2 The objective 56

3.3 The data 57

3.3.1 The primary data 57

3.3.2 The secondary data 58

3.4 Research methodology 58

3.4.1 Subjects 58

3.4.2 Experimental design 60

3.4.3 Methods of data analysis 65

4. CHAPTER 4 : RESULTS 70

4.1 Lumbar spine ranges of motion 70

4.2 Pain sensitivity 70

4.3 Pain intensity 70

4.4 Pain quality 71

4.5 **Blood** 71

4.6 **Demographic data** 116

5. CHAPTER 5: DISCUSSION 117

5.1 **Introduction** 117

5.2 **Objective data** 117

5.2.1 **Lumbar spine ranges of motion** 117

5.2.1.1 Intra-group comparison 117

5.2.1.2 Inter-group comparison 118

5.2.2. **Algometric readings** 118

5.2.2.1 Intra-group comparison 118

5.2.2.2 Inter-group comparison 119

5.2.3 **Interpretation of objective findings** 119

5.3 **Subjective data** 121

5.3.1 **Numerical Rating Scale 101** 121

5.3.1.1 Intra-group comparison 121

5.3.1.2 Inter-group comparison 121

5.3.2 **Short-form McGill Pain Questionnaire** 121

5.3.2.1 Intra-group comparison 121

5.3.2.2 Inter-group comparison 122

5.3.3 **Oswestry Back Disability Index** 122

5.3.3.1 Intra-group comparison 122

5.3.3.2 Inter-group comparison 122

5.3.4 Interpretation of subjective data 123

5.4 Blood and lymphocyte profiles 124

5.4.1 Intra-group comparison 124

5.4.2 Inter-group comparison 124

5.4.3 Interpretation of blood and lymphocyte profiles 125

5.5 Demographic data 126

5.6 Comment 126

6. CHAPTER 6 : CONCLUSIONS AND RECOMMENDATIONS 128

7. REFERENCES 130

LIST OF TABLES

Table 4.1.1 (a)	Degrees of forward flexion in the experimental and control groups at each consultation.	72
Table 4.1.1 (b)	Wilcoxon's Signed Rank Test for forward flexion.	73
Table 4.1.1 (c)	Mann-Whitney U-test for forward flexion.	73
Table 4.1.2 (a)	Degrees of extension in the experimental and control groups at each consultation.	74
Table 4.1.2 (b)	Wilcoxon's Signed Rank Test for extension.	75
Table 4.1.2 (c)	Mann-Whitney U-test for extension.	75
Table 4.1.3 (a)	Degrees of left rotation in the experimental and control groups at each consultation.	76
Table 4.1.3 (b)	Wilcoxon's Signed Rank Test for left rotation.	77
Table 4.1.3 (c)	Mann-Whitney U-test for left rotation.	77

Table 4.1.4 (a) Degrees of right rotation in the experimental and control groups at each consultation. **78**

Table 4.1.4 (b) Wilcoxon's Signed Rank Test for right rotation. **79**

Table 4.1.4 (c) Mann-Whitney U-test for right rotation. **79**

Table 4.1.5 (a) Degrees of left lateral flexion in the experimental and control groups at each consultation. **80**

Table 4.1.5 (b) Wilcoxon's Signed Rank Test for left lateral flexion. **81**

Table 4.1.5 (c) Mann-Whitney U-test for left lateral flexion. **81**

Table 4.1.6 (a) Degrees of right lateral flexion in the experimental and control groups at each consultation. **82**

Table 4.1.6 (b) Wilcoxon's Signed Rank Test for right lateral flexion. **83**

Table 4.1.6 (c) Mann-Whitney U-test for right lateral flexion. **83**

Table 4.2.1 (a) Algometric readings in the experimental and control groups at each consultation. **84**

Table 4.2.1 (b) Wilcoxon's Signed Rank Test for algometric readings. **85**

Table 4.2.1 (c) Mann-Whitney U-test for algometric readings. **85**

Table 4.3.1 (a) Numerical Rating Scale 101 values in the experimental and control groups at each consultation. **86**

Table 4.3.1 (b) Wilcoxon's Signed Rank Test for the Numerical Rating Scale 101. **87**

Table 4.3.1 (c) Mann-Whitney U-test for the Numerical Rating Scale 101. **87**

Table 4.3.2 (a) Short-form McGill Pain Questionnaire values in the experimental and control groups at each consultation. **88**

Table 4.3.2 (b) Wilcoxon's Signed Rank Test for the Short-form McGill Pain Questionnaire. **89**

Table 4.3.2 (c) Mann-Whitney U-test for the Short-form McGill Pain Questionnaire. **89**

Table 4.4.1 (a) Oswestry Back Disability Index in the experimental

	and control groups at each consultation.	90
Table 4.4.1 (b)	Wilcoxon's Signed Rank Test for the Oswestry Back Disability Index.	91
Table 4.4.1 (c)	Mann-Whitney U-test for the Oswestry Back Disability Index.	91
Table 4.5.1 (a)	Haemoglobin levels (g/dL) in the experimental and control groups at each consultation.	92
Table 4.5.1 (b)	Wilcoxon's Signed Rank Test for haemoglobin levels.	93
Table 4.5.1 (c)	Mann-Whitney U-test for haemoglobin levels.	93
Table 4.5.2 (a)	White blood cell count (cells/microliter) in the experimental and control groups at each consultation.	94
Table 4.5.2 (b)	Wilcoxon's Signed Rank Test for the white blood cell count.	95
Table 4.5.2 (c)	Mann-Whitney U-test for the white blood cell count.	95

Table 4.5.3 (a) Platelet count (no/cubic mm) in the experimental and control groups at each consultation. **96**

Table 4.5.3 (b) Wilcoxon's Signed Rank Test for the platelet count. **97**

Table 4.5.3 (c) Mann-Whitney U-test for the platelet count. **97**

Table 4.5.4 (a) Absolute count (cells/microliter) in the experimental and control groups at each consultation. **98**

Table 4.5.4 (b) Wilcoxon's Signed Rank Test for the absolute count. **99**

Table 4.5.4 (c) Mann-Whitney U-test for the absolute count. **99**

Table 4.5.5 (a) CD3 count(no/cubic mm) in the experimental and control groups at each consultation. **100**

Table 4.5.5 (b) Wilcoxon's Signed Rank Test for the CD 3 count. **101**

Table 4.5.5 (c) Mann-Whitney U-test for the CD 3 count. **101**

Table 4.5.6 (a) CD 4 count (no/cubic mm) in the experimental and control groups at each consultation. **102**

Table 4.5.6 (b) Wilcoxon's Signed Rank Test for the CD 4 count. **103**

Table 4.5.6 (c) Mann-Whitney U-Test for the CD 4 count. **103**

Table 4.5.7 (a) CD 8 count (no/cubic mm) in the experimental and control groups at each consultation. **104**

Table 4.5.7 (b) Wilcoxon's Signed Rank Test for the CD 8 count. **105**

Table 4.5.7 (c) Mann-Whitney U-test for the CD 8 count. **105**

Table 4.5.8 (a) CD 2 count (no/cubic mm) in the experimental and control groups at each consultation. **106**

Table 4.5.8 (b) Wilcoxon's Signed Rank Test for the CD 2 count. **107**

Table 4.5.8 (c) Mann-Whitney U-test for the CD 2 count. **107**

Table 4.5.9 (a) CD 19 count (no/cubic mm) in the experimental and control groups at each consultation. **108**

Table 4.5.9 (b) Wilcoxon's Signed Rank Test for CD 19 count. **109**

Table 4.5.9 (c) Mann-Whitney U-test for the CD 19 count. **109**

Table 4.5.10 (a) CD 56 count (no/cubic mm) in the experimental and control groups at each consultation. **110**

Table 4.5.10 (b) Wilcoxon's Signed Rank Test for the CD 56 count. **111**

Table 4.5.10 (c) Mann-Whitney U-test for the CD 56 count. **111**

Table 4.5.11 (a) CD 45 RA count (no/cubic mm) in the experimental and control groups at each consultation. **112**

Table 4.5.11 (b) Wilcoxon's Signed Rank Test for the CD 45 RA count. **113**

Table 4.5.11 (c) Mann-Whitney U-test for the CD 45 RA count. **113**

Table 4.5.12 (a) CD 29 count (no/cubic mm) in the experimental and control groups at each consultation. **114**

Table 4.5.12(b) Wilcoxon's Signed Rank Test for the CD 29 count. **115**

Table 4.5.12 (c) Mann-Whitney U-test for the CD 29 count. **115**

Table 4.6.1 Demographic data. 116

LIST OF GRAPHS

Graph 4.1.1	Mean values for forward flexion.	**72**
Graph 4.1.2	Mean values for extension.	**74**
Graph 4.1.3	Mean values for left rotation.	**76**
Graph 4.1.4	Mean values for right rotation.	**78**
Graph 4.1.5	Mean values for left lateral flexion.	**80**
Graph 4.1.6	Mean values for right lateral flexion.	**82**
Graph 4.2.1	Mean values for the Algometric readings.	**84**
Graph 4.3.1	Mean values for the Numerical Rating Scale 101.	**86**
Graph 4.3.2	Mean values for the Short-form McGill Pain Questionnaire.	**88**
Graph 4.4.1	Mean values for the Oswestry Back Disability Index.	**90**

Graph 4.5.1 Mean values for haemoglobin levels. **92**

Graph 4.5.2 Mean values for white blood cell count. **94**

Graph 4.5.3 Mean values for platelet count. **96**

Graph 4.5.4 Mean values for absolute count. **98**

Graph 4.5.5 Mean values for the CD 3 count. **100**

Graph 4.5.6 Mean values for the CD 4 count. **102**

Graph 4.5.7 Mean values for the CD 8 count. **104**

Graph 4.5.8 Mean values for the CD 2 count. **106**

Graph 4.5.9 Mean values for the CD 19 count. **108**

Graph 4.5.10 Mean values for the CD 56 count. **110**

Graph 4.5.11 Mean values for the CD 45 RA count. **112**

Graph 4.5.12 Mean values for the CD 29 count. **114**

CHAPTER 1

1. INTRODUCTION

Low back pain constitutes one of the main health problems in industrialised countries, resulting in substantial financial costs (Paquet et al. 1994). Low back pain has recently become a popular topic for epidemiological investigations as a result of the enormous costs of treatment and disability of this condition (Burton and Cassidy 1992:2). According to these authors up to eighty percent of the population will experience low back pain at some time in their life. Although a small but significant number of those affected develop chronic pain resulting in long-term disability, it is this group that is responsible for the most of the financial costs relating to low back pain.

Spinal adjustive therapy is one of the oldest as well as one of the most common forms of treatment used for patients suffering with low back pain (Giles 1989:160). Clinical studies have shown spinal manipulative therapy to be consistently more effective than any of the array of comparison treatments (Anderson et al. 1992 and Meade et al. 1995). Results of the study conducted by Meade et al. (1995), concluded that for patients with low back pain, in whom manipulation was not contraindicated, chiropractic almost certainly was worthwhile in respect of long-term improvement in comparison with hospital outpatient management. There is, therefore economic support for the use of

chiropractic in low back pain, though the obvious clinical improvement in pain and disability attributable to chiropractic treatment is in itself an adequate reason for considering chiropractic.

According to the Kirkaldy-Willis et al. (1992:121) classification, examples of mechanical low back pain include posterior facet syndrome, sacro-iliac syndrome, Maigne's syndrome, disc herniation, facet and disc degeneration, central and lateral canal stenosis and myofascial pain dysfunction syndrome. The abovementioned examples result in spinal dysfunction (subluxation) which are characterized by one or more of hyperaemia, congestion, oedema, minute haemorrhages, fibrosis, local eschaemia, atrophy and ultimately rigidity and adhesions which form not only in the joint capsules, but also in the ligaments, tendons and muscles (Gitelman 1975 :285). This may result in nerve irritation or compression and a subsequent increase in neuronal activity through facilitation (Gatterman 1990:41).

According to Korr (1979) proper sympathetic nervous system function is dependant on continuous, accurate sensory input from the musculoskeletal system to the central nervous system. When types of musculoskeletal dysfunction occurs, the sensory input to the central nervous system is altered, which may result in segmental sympathetic hyperactivity. Neurological segmental relationships between somatic and visceral structures determine which segments of the sympathetic nervous system become hyperactive. Those tissues innervated by the hyperactive segment of the sympathetic

nervous system are adversely affected through changes in perfusion, metabolism, and/or visceral activity, depending on the specific organ or tissue involved (Leach 1994:315).

There is anatomical evidence to support the hypothesis that the nervous system modulates the activity of the immune system. It has been demonstrated that the thymus, the spleen, lymph nodes, bone marrow and gut-associated lymphiod tissue all receive sympathetic noradrenergic innervation (Felten et al. 1987). The huge diversity of the immune system and the numerous connections between the nervous and the immune system suggest that some modulatory effects can occur (Allen 1993).

Brennan et al. (1994) were the first to report on lymphocyte profiles in patients diagnosed with chronic low back pain. Their findings of a lower percentage of Natural Killer cells in patients diagnosed with chronic low back pain, confirms earlier findings by Lohr et al. (1990), that patients with musculoskeletal problems have a lower percentage of Natural Killer cells than do asymptomatic subjects.

If chiropractic treatment can affect the connections between the nervous system and the immune system and thereby influence this modulation, then it may have a beneficial effect on immune status, although this has yet to be demonstrated in clinical trials.

Thus it is the purpose of this study to determine if the treatment of patients suffering from mechanical low back pain with spinal manipulative therapy is effective and whether any significant changes in immune status on a cellular level occur.

CHAPTER 2

2. REVIEW OF THE RELATED LITERATURE

2.1 INTRODUCTION

The idea of "body tone" or homoeostasis has been stated to be sheer quackery by more than a majority of medical investigators throughout this century and for plausible reasons. Medical researchers have sought and succeeded in determining the causative agents in many diseases, most of which responded well to antibiotics and other therapies. (Leach 1994: 293).

Chiropractic was originally based on the idea that health and disease are dependant on nervous system function. Palmer (1910:19) stated that "The amount of nerve tension determines health and disease. In health there is normal tension, known as tone, the normal activity, strength and excitability of the various organs and functions as observed in a state of health. The kind of disease depends on what nerves are too tense or too slack." One aspect of this, is the effect of nervous system activity in maintaining immune competence.

It has been suggested that spinal manipulation affects cells of the immune system (Korr 1986, Spector 1987). However, there is little experimental or clinical

evidence to support these suggestions. For reasons that are not entirely clear, the neurosciences and immunology evolved without seriously considering the possibility of interactions between these systems that could mutually influence their respective functions. However, within the past 15 years, research concerned with the relationships between brain, behaviour and immunity have expanded rapidly (Ader et al. 1995).

If psychosocial stresses can influence immunologic competence by acting through neuroendocrine or direct neural mechanisms, the question arises why could the stress due to intervertebral subluxation not do it as well? Reviews of medical studies have shown that the effects of the intervertebral subluxation are wide-ranging, in some cases possibly altering neural transmissions. What is important for the chiropractic profession is that, regardless of the specific mechanisms involved, there are pathways for neural modulation of immunological competence. (Leach 1994: 315.)

2.2 MECHANICAL LOW BACK PAIN

2.2.1 INCIDENCE AND PREVALENCE OF MECHANICAL LOW BACK PAIN

Back pain, particularly low back, has plagued humanity for thousands of years. It is estimated that in the United States alone, 75 million people suffer from back pain, and there are seven million new victims each year. Of these, five million are partly disabled and two million are unable to work at all. (Cox 1985: 10).

According to Burton and Cassidy (1992:2), low back pain has a lifetime prevalence of between sixty and eighty percent for any population, and between twenty and thirty percent of the population are suffering from it at any given time. It is, after the common cold, the most common health problem in the United States. (Cats-Baril and Frymoyer 1991; 1:95).

Low back pain is the diagnosis in ten percent of all chronic health problems. Impairments of the back are the most frequent cause of activity limitation in persons under 64 years of age. In subjects aged 25 to 44 years, a decrease in work capacity was caused by low back pain. An average of 28,6 days per 100 workers are lost each year and there is an average of nine days confinements to bed (Cox 1985:9).

Low back pain is a disease that needs a great deal of study and understanding, for it remains an enigma of medical science, for the patient, the insurance carrier, attorneys, employers and family members (Cailliet 1988:v). It is vital to understand the socio-economic importance of this disease, the underlying cause of it, try to find better methods of treatment for it, as well as subject the old methods to critical analysis (Nachemson 1976).

The magnitude of a low back pain problem is financially formidable (Cailliet 1988:v). Five billion dollars were spent in the United States in 1980 on the diagnosis and treatment of low back pain and another ten billion dollars were spent on disability compensation, lawsuits and workman's compensation. The cost for treatment of low back pain increases faster than that of any other ailment of the human race (Cats-Baril and Frymoyer 1991:94).

Although most attacks of back pain remit either spontaneously or after treatment, there is a high incidence of recurrence (Sims-Williams et al. 1979). This represents a significant problem, which is complicated by the fact that the most common cause of low back pain (viz: Facet syndrome Sacro-iliac and Myofascial syndrome), are frequently overlooked, as abnormalities of these conditions are not often demonstrated on X-rays (Bernard and Kirkaldy-Willis 1987). After three months of low back pain, only five percent of patients have persisting symptoms, yet it is this population that accounts for eighty five percent

of the cost in terms of compensation and loss of work due to low back pain (Frymoyer 1988; Burton and Cassidy 1992:3).

2.2.2 AETIOLOGY OF LOW BACK PAIN

It is only through a better understanding of pain and its pathophysiology that responsible decisions can be made regarding its treatment (Weinstein 1991:594).

The human vertebral column is a remarkable structure consisting of many parts, which should be considered as an integrated unit. It combines strength and flexibility by alternately interposing rigid bony vertebra with deformable cartilaginous discs which live because of movement (Hirsch et al. 1963). Lewin et al. (1962) and Hirsch et al. (1963) pointed out that the basic anatomical and functional unit of the vertebral column is the articular triad consisting of the fibrocartilaginous intervertebral joints and the two synovial zygapophyseal joints. The motion segment can be divided into anterior and posterior elements. The anterior elements includes the vertebral body, the disc and the anterior and posterior longitudinal ligaments. It provides stability and shock absorption. The posterior elements are composed of the pedicles, the zygapophyseal joints, and the posterior ligamentous and muscular attachments. The posterior elements control the spinal movements. (Anderson et al. 1992).

According to Cox (1979) each lumbar vertebra is capable of five basic movements, viz. flexion, extension, lateral bending, rotation and circumduction. This normal anatomical range of mechanical movement is a prerequisite to efficient, pain-free movement. He further states that a joint capable of producing these movements in a pain-free manner is a healthy articulation. Among the wide variety of pathological conditions that can affect the lumbar spine are congenital malformations, fractures, infections and neoplastic diseases, inflammatory, metabolic and various miscellaneous disorders.

However, certain pathological conditions that underlie common forms of low back pain syndrome and which involve only minor structural abnormalities occur very frequently and are referred to as mechanical low back pain. These disorders involve altered biomechanics of the spine and result in minor aberrations of structure or in injury of the lumbar spine. Although these are usually due to minor injuries, they can have quite major short and long term consequences. (Bogduk and Twomey 1991:152-153).

Despite the apparent ignorance in determining the exact aetiology of back pain in a single individual, there has been substantial biomechanical, physiological and psychosocial research which has produced information concerning the risks predisposing to back pain and disability in the population.

According to the Kirkaldy-Willis' classification (1992:121) examples of mechanical low back pain include posterior facet syndrome; sacro-iliac syndrome; Maigne's syndrome; disc herniation; facet and disc degeneration; central and lateral canal stenosis and myofascial pain dysfunction syndrome.

The zygapophyseal joint facet syndrome and some muscle syndromes are common, but because these lesions usually do not demonstrate abnormalities radiographically they are frequently overlooked. (Bernard and Kirkaldy-Willis 1987).

According to Mennel (1964:18) the difficulty in diagnosing and treating back pain results in part from the failure of physicians to think in mechanical terms when approaching the patient with a back complaint.

Three main mechanisms by which pain may arise are:

(1) Mechanical pinching of synovial fold tissue, which may result in traction on the pain sensitive tissues and tissue damage with cell rupture. The subsequent release of pain producing substances, results in nerve impulses arising from the nociceptors. This accounts for the low back pain sensation and discomfort that the patient feels. (Giles 1989:159).

(2) Traumatic synovitis causing ischaemia with the genesis of ischaemic pain. (Giles 1989:159).

(3) Myofascial sources of pain. (Kirkaldy-Willis et al. 1992:122).

According to Bogduk and Twomey (1991:34), intra-articular structures of the lumbar zygapophyseal joints project only five millimetres into the joint cavity. Three types of intra-articular structures are identified in the lumbar joints, ie. adipose tissue pads, fibro-adipose meniscoid and connective tissue rims (Bogduk and Twomey 1991:34).

In addition to the general nutritive and lubricating functions of the synovial membrane, synovial folds have a packing or "space-filling" function which allows movement of adjacent structures. Bogduk and Engel (1984) state that they also provide greater stability and help to distribute the load on the joint over a greater area.

Therefore, it seems reasonable to speculate that mechanical "nipping" of synovial folds or traumatic synovitis with chemical irritation of nerve endings due to the release of noxious chemical stimuli in the synovial fold, could result in pain. The entrapment of "meniscoid inclusions" may mechanically interfere with movement leading to pain and muscle spasm. When large fibrous tips of synovial folds are present, it is conceivable that these fibrous structures could also cause mechanical dysfunction with "locking" of joint at that level (Giles 1989:159).

Histological evidence that showed nipping of a highly vascular intra-articular

synovial fold with a fibrotic tip projecting between the hyaline articular cartilage surfaces of osteoarthritic zygapophyseal joint was demonstrated by Giles (1989:160).

Kirkaldy-Willis (1988:94) believe impingement is accompanied by oedema, synovitis and distension of the capsule causing nerve root irritation. Movement could stress the well-innervated joint capsule at the point where the meniscoid attaches to it. A reflex muscle spasm would then serve to restrict motion at the joint (Rahlmann 1987). It is thought that chronic inflammation and fibrosis in the synovium and capsule of the zygapophyseal joints may produce persistent severe back pain (Giles 1989:159).

According to Gitelman (1975:278), "subluxation" (spinal dysfunction) is a process and not a static condition. Associated changes include hyperaemia, congestion, oedema, minute haemorrhages, fibrosis, local ischaemia, atrophy and ultimately rigidity and adhesions which form not only in the joint capsules but also in the ligaments, tendons and muscles. This has been confirmed in a study by Jayson et al. (1984) of blood fibrinolytic activity in patients with severe chronic back pain. According to this study, patients showed evidence of defective fibrinolysis, which could possibly, according to the authors, be associated with fibrin deposition and scar formation and therefore be responsible for the development and/or perpetuation of chronic inflammation and scarring at sites of damage in the spine.

Kirkaldy-Willis et al. (1992:49-53) expounded on the relationship between three aspects in the pathogenesis of low back pain, namely emotional factors (including emotional trauma), changes in muscle, and changes in the facet joints and intervertebral disc. The postulate describes how emotional disturbance (including stress, anxiety, fear, resentment and depression) produces local areas of vasoconstriction in muscle, which, together with sustained muscle contraction and accumulation of metabolites results in muscle fatigue. This causes changes in the recruitment of motor units in muscle, creating altered patterns of muscle contraction, commonly thought to be in the multifidus. Long-term changes in muscle result in painful, restricted movement - learned restriction as well as fibrosis, which ultimately leads to the chronic pain syndrome.

Some authors suggest that Substance P (SP) may have a role in chronic degeneration of the spinal motion segment because of its presence in the dorsal root ganglion, disc annulus, facet joints, and blood plasma. (Weinstein, Claverie et al. 1988; Weinstein, Pope et al. 1988).

The structures in the lumbar spines that receive a nociceptive nerve supply are the zygapophyseal joints(synovial membrane and capsule), the ligaments of the posterior elements, the paravertebral muscles, the dura-mater, the anterior and posterior longitudinal ligaments and the intervertebral disc. Each of these structures has been implicated as a source of low back pain. (Bogduk and Twomey 1991:152).

Given that various structures in the lumbar spine have been shown to be capable of producing low back pain, it is important to realise that in each case the mechanism involved is the stimulation of nerve endings in the affected structure. There are two mechanisms by which the nerve endings may be stimulated, i.e. mechanical and chemical irritation. (Bogduk and Twomey 1991:152).

Chemical irritation occurs in inflammatory diseases or follows tissue damage. Mechanical irritation on the other hand, involves stretching and compressing (e.g.synovial pinching) of connective tissue. Exactly how mechanical irritation causes pain remains obscure, but a plausible explanation is that when an array of collagen fibres (in a ligament, periosteum or joint capsule) is placed under tension, it deforms and closes the available space between individual collagen fibres. Nerve endings within the array would then be stimulated by being squeezed between the encroaching collagen fibres (Bogduk and Twomey 1991:153). Homewood (1977:73) is in agreement with Bogduk and Twomey and states that mechanical, chemical and mental stresses create the structural distortions that interfere with the nerve supply and result in altered function to the point of demonstrable cellular changes known as pathology.

Homewood (1977:89) further states, "The site of the actual subluxation is likely to be pre-ordained by the structural weakness of past history of injury, occupational or recreational abuses which may have produced frank trauma or merely microtrauma which tends to summate, or by mechanical force being

concentrated upon a localised area."

Thus from the above it can be concluded that spinal joint fixation compromises neural elements, which produces irritation and compression of these structures. Nerve irritation results in an increased neuronal activity through facilitation, while the pressure that produces nerve compression leads to tissue degeneration. (Gatterman 1990:41).

Korr (1979) and (1986) has written extensively on the clinical significance of the facilitated state due to nerve irritation. His definition of the facilitated state is that the spinal cord segments adjacent to the fixed vertebral motion segment have at least some of the neurons mediating sensory, motor and autonomic function maintained in a state of hyper-excitability.

This facilitation of anterior horn cells affects motor outflow, resulting in sustained muscular tensions, postural asymmetries and limited, painful motion. The richly innervated muscles, tendons, ligaments and joint capsules may subsequently produce intense and exaggerated streams of afferent impulses with resultant pain. Facilitation of the posterior horn cells expedites impulses to the central nervous system, including the higher centres, magnifying noxious or painful stimuli. (Gatterman 1990:41). Facilitation of the lateral horn cells effects autonomic outflow, which may have deleterious effects on target tissues, including the viscera, blood vessels and glands. Areas of sympathetic

hyperactivity correlate well with segmental distribution and existing musculo-skeletal strain, trauma, deep and superficial tenderness and electromyographic activity of paraspinal muscles (Gatterman 1990:41). As the nervous and immune system are anatomically linked, spinal joint fixations could possibly influence the immune system as discussed in paragraph 2.5.1.

2.2.3 MECHANISM OF JOINT FIXATION

More commonly recognised than nerve irritation within the chiropractic profession, has been the hypothesis that the subluxation complex causes nerve compression (Leach 1994:49). Neural structures normally have ample room as they exit the intervertebral foramen, being protected by loose areolar tissue and adipose tissue. However, several factors may compromise this margin of safety. The most widely acknowledged cause of nerve compression at the intervertebral foramen has been intervertebral disc pathology. Inflammation and osteophytic formation on the zygapophyseal joints may significantly alter the size of the intervertebral foramen and entrap the nerve (Anderson 1985).

Sunderland (1978:160) states that the veins, along with the spinal nerves, are primary structures passing through the intervertebral foramen. These may be affected by the compression, restricted movement (fixation) and inflammation associated with the subluxation complex. Resultant venous congestion with

impaired return of venous blood that results in oedema, may then interfere with neural transmission.

The cause of restricted intervertebral mobility or joint fixation has generated much speculation. Some possible theories that merit further investigation include meniscoid entrapment, displaced intervertebral disc fragments (disc disruption), segmental or intersegmental muscle spasm and periarticular connective tissue adhesions. The two questions that need to be addressed for each theory are:

(a) How does each mechanism restrict intervertebral movement?

(b) How does a high velocity manipulation restore movement and relieve symptoms? (Rahlman 1987).

Possible answers to a) above include:

(1) Meniscoid entrapment - as described previously.

(2) Displaced intervertebral fragments (disc disruption) - According to Cyriax (1977:57-66) the only way a joint can become suddenly fixed within its normal range, is due to an internal derangement of the disc i.e. "A broken fragment of the disc displaced and jamming the joint."

A number of authors disagree and point out that joint locking occurs in the spine at joints that have no discs, i.e. Atlanto-occipital and Atlanto-axial joints (Rahlmann 1987 and Bourdillon, et al. 1992: 305). This emphasizes the possibility that more than one type of mechanism may be involved in joint locking, and that different mechanisms be regionally variable. (Rahlmann 1987).

(3) Muscle spasm, as a cause of acute joint locking, has been implicated by Korr (1975: 188). The possible mechanism that could induce a spasm in the para-vertebral muscles, are trauma-induced spasm of splinting. (Rahlmann 1987).

Where pain originates in the muscles, is not fully understood. Ischaemia has been implicated as a cause. The accumulation of metabolites such as substance P, kinins, prostaglandins, histamine, lactate and numerous others have been considered a cause of muscle nociception. Accumulation of tissue metabolites has been attributed to a sustained muscular contraction or to mechanical trauma to the muscle. (Cailliet 1988:71).

(4) Periarticular connective tissue adhesions - An often repeated explanation for joint movement restriction has been "fibrous adhesions". Two different types of adhesions occur. Those associated with a joint which

first undergoes trauma, which is followed by inflammation and repair, which in turn leads to scar tissue formation. A second process leading to adhesions is joint immobilisation, without inflammation or trauma. (Rahlmann 1987).

(5) The inequality of ligament tension, due to shortening or contracture formation, has also been implicated as a cause of intervertebral joint fixation. (Gatterman 1990:45).

The term 'deconditioning syndrome' has been applied to the cumulative disuse changes produced in the chronically disabled patient suffering from spinal dysfunction. It is initially produced by the immobilisation and inactivity attendant on injury. It is supplemented by disruption of spinal soft tissue and scarring resulting from a surgical approach or repetitive microtrauma. As pain perception is enhanced, learned protective mechanisms lead to a vicious cycle of inactivity and disuse. As physical capacity decreases the likelihood of fresh sprains or strains to unprotected joints, muscles, ligaments and discs increase.

These inevitable alterations of pain and function are perceived by the patient as a 'recurrence' or 'reinjury'. (Haldeman 1992:535).

Answer to (b):

The exact mechanism by which manipulation relieves pain remains a subject of significant debate. The more prominent theories are as follows:

(1) Change in pain threshold - Terret and Vernon (1984) attempted to investigate this phenomenon by measuring tolerance to electrically induced pain in paraspinal tissues in two groups, one group receiving joint play, where the investigator placed both thumbs over the paraspinal tissues bilaterally and produced a posterior-anterior joint springing action from T1 down to T10, and the other group joint play and spinal manipulative therapy.

Although both groups showed increases in pain tolerance, the increase was significantly higher (140%) in the group undergoing manipulation. The possibility that there may be a release of endorphin following spinal manipulative therapy, has been raised but not confirmed (Haldeman 1993). According to Geiringer et al. (1988:450-451) spinal manipulation could possibly produce an afferent signal to the cord and directly diminishes pain awareness by a gate control effect. They further state that the restoration of normal spinal motion is thought to result in the elimination of pain secondary to disturbed biomechanics.

(2) Release of muscle spasm - Haldeman (1993) reported normalisation of magnetically induced muscle contraction by cortical evoked responses following manipulation. They suggest that this may reflect changes in muscle spindle activity. All forms of manipulation are thought to interfere with abnormal muscular contraction, either by production of afferent stimuli which attenuate a hyper-excitable gamma system, or by elimination of proprioreceptive input which stimulates the gamma system as a result of the muscle lengthening. In addition, thrust, and possibly articulatory and isometric techniques, can stimulate Golgi tendon organ input (Korr, et al. 1947). The net result of muscle relaxation is that the vertebra will regain normal play and active and passive range of motion and the forces needed to produce them will be normalised. Pain is thought to be reduced as a result of return of function. (Geiringer et al. 1988:85).

(3) Reduction of disc protrusion - According to Cyriax (1977:59) the goal of spinal manipulation is to put a disc fragment back into place and therefore restore movement to a "jammed joint". The proposed mechanism of disc derangement is outlined by Sandoz (1976). The above author also describes the role of a rotatory manipulative thrust coupled with traction in returning the fragment to its 'normal' position. Side posture long axis traction is used to open the disc space and provide a suction mechanism for the fragment.

However, Bourdillon et al. (1992: 303) observes that if sequestrated nuclear material is returned to its normal space by manipulation, what prevents it from returning to the preformed fissure it protruded into Rahlmann (1987) concludes that the disc fragment sequestration theory requires that all cases of joint locking must be accompanied by some degree of annulus degeneration. He states it is illogical to believe this is the case.

Shekelle et al. (1992) state that the spinal manipulation has not been shown to reduce a herniated nucleus pulposus physically. In fact, two studies cited by Shekelle et al. (1992) showed no difference myelographically in disc protrusion before and after manipulation. However, many patients reported an improvement in symptoms despite the apparent absence of a change in their disc protrusion. Thus, although many different theories exist about the effect of manipulation has on a disc protrusion, the authors do agree that spinal adjustment can offer symptomatic relief.

(4) Increased range of motion (ROM) - This is the most popular theory regarding the effect of manipulation. It has been incorporated into theories of chiropractic, medical, osteopathic and physical therapy (Haldeman 1993). Waagen, et al. (1986) demonstrated an increase in gross range of motion of the lumbar spine following manipulation.

According to Geiringer et al. (1988:28) one effect of manipulation for which there is no substitute, is the reversal of the restricted joint movement. It is the restoration of normal joint movement that has earned chiropractic its unique place in health care systems.

(5) Shekelle et al. (1992) states that manipulation of the lumbosacral spine has long been known to give relief to symptoms in a large number of patients, with a very low risk of complications, but the mechanism of action is ill defined. However, in a group of patients manipulated during an operation in the lateral position, the laminae were seen to move apart, stretching the fibres of the ligamentum flavum and the fibrous joint capsule. Therefore it is quite conceivable that as the capsular ligaments are stretched during a rotatory manipulation, the synovial fold could be retracted from between opposing facet surfaces.

(6) Psychological effect of manipulation - there is growing recognition of the close relationship between psychological and psychosocial factors and back pain and disability. The strong enthusiasm and positive attitude of both patients and practitioners to manipulation may do more to reduce pain and disability than some of the other proposed mechanisms. (Haldeman 1993).

2.3 THE EFFICACY AND COST-EFFECTIVENESS OF SPINAL MANIPULATIVE THERAPY

In a comparison of chiropractic, medical, and osteopathic care for work-related sprains and strains, Johnson et al. (1989) found fewer work days were lost, and lower amounts of disability compensation and provider costs were paid when chiropractic treatment (spinal manipulative therapy) was administered. In a comparison of health care costs for chiropractic and medical patients, Stano (1993), suggested significant cost-savings for chiropractic users.

While the first descriptive report of manipulation can be dated to 1930, the majority of clinical trials have been published since 1975. The majority of analytical studies which have addressed the short-term effect and the potential mechanism involved in manipulation, have been published in the past decade. (Vernon 1996).

Several major reviews of clinical trials of manipulation of low back pain and two meta-analysis have appeared within the last five years. Most of these trials involved acute or subacute low back pain (Shekelle et al. 1992; Anderson et al. 1992; Bronfort 1989:415). These panels found that sufficient evidence existed to recommend spinal manipulation as a treatment of acute low back pain without radiculopathy within the first month of symptoms. Manipulation appears to hasten recovery in the majority of subjects who have received it in these clinical

trials, while only a small minority of back pain sufferers failed to achieve resolution of their painful episode.

Evans et al. 1978 were the first to explicitly address back pain sufferers with more long standing pain. Their trial was undertaken to study a small number of patients; 15 in the manipulation group(group A) and 17 in the control group (group B). In this crossover design study, group A received spinal manipulation first, then medical care with analgesics while group B received the reversed protocol. Statistically significant reduction of pain and an increase of lumbar flexion was obtained in group A during the spinal manipulative phase as compared to group B in the analgesic phase. The two manipulative treatments (first in group A versus second in group B) were associated with similar ratings but the two control treatment periods were associated with ratings which were not only dissimilar, but different by a highly significant degree. The authors felt that this paradox could be explained by a carry-over effect in group A from the manipulative treatment period of the first three weeks to the control period.

Coxhead et al. 1981 used a large number of chronic subjects (N = 322) with low back pain and divided them randomly to 16 different treatment combinations, comparing traction, spinal manipulative therapy, exercise and corsets. At four weeks 78% of all the subjects said they had improved, whether or not they had received a particular treatment. Improvements at four weeks on the pain analogue scale tended to be greater in those receiving manipulation treatment,

which showed a statistically significant difference over the other treatments. The results in terms of return to work or normal activities by the end of the four-week treatment period showed that those having traction or manipulation had done better than those not. Further factorial analysis confirmed that combinations of spinal manipulative therapy and exercise produced the optimal results.

The first trial by Waagen et al. (1986), which compared active manipulation to a sham procedure in patients with low back pain of longer than 3 weeks duration. The spinal manipulative therapy group (10 patients) achieved statistically greater reduction in pain post-treatment and at two week follow- up than the controls (9 patients). Scores on a global index of spinal range of motion and straight leg raising were also significantly better in the spinal manipulative therapy group at the two-week follow-up.

More recent studies by Triano (1995), compared chiropractic manipulation with sham manipulation in a back education programme. From a total of 366 patients, 209 agreed to participate. These patients were assigned for treatment using a block randomization scheme, constructed before the study was begun. Treatment allocation resulted in patient placement into one of three groups: (1) high velocity low amplitude spinal manipulation (HVLA), (2) high velocity low force mimic (HVLF) and (3) a back education programme (BEP). 170 remaining patients completed 7 or more of the rescheduled treatment sessions.

Visual analog score measures demonstrated the largest clinically relevant improvement for the HVLA group with a decline in mean score of 24,6% which remained stable after a two-week follow-up. The HVLF mimic group showed an initial mean decline of 17,6% that increased to 1,94% during the therapeutic withdraw period. Behaviour of the VAS scores for the BEP group paralleled the response of the mimic group which recovered by an additional 4.5% during the withdrawal period. Significantly pain reduction was found in the spinal manipulative therapy groups as compared to the back education group after two weeks of treatment. No difference between groups were found on Oswestry Index scores although a trend favouring chiropractic spinal manipulative therapy was shown.

Meade et al. (1990) and Meade et al. (1995), using changes in total Oswestry questionnaire scores and in scores for pain and patient satisfaction. The progress of 741 low back pain patients (undergoing either chiropractic or hospital treatment) for levels of pain, daily activities and satisfaction with their treatment were compared. The numbers revealed that over the 3 years the study was conducted, 29% more improved under chiropractic care, than those treated under hospital care. Chiropractic patients also expressed greater general satisfaction with their treatment, slept better and were able to sit for longer periods. The authors also noted that other scores (personal care, lifting, walking, standing, sex life, social life and travelling) nearly all improved to a greater extent in the patients treated with chiropractic, although most of the difference was in terms of pain.

2.4 THE IMMUNE SYSTEM

The contemporary view of the immune system gives it three functions: defence, homeostasis and surveillance. The first is involved in resistance to infection by micro-organisms, the second the removal of 'worn-out self' components, and the third with the perception and destruction of mutant cells. (Bellanti 1979: 14-21 and Guyton and Hall 1996:445-446).

The immune system may be regarded as having two component functions: non-specific immunity and specific immunity.

(1) Non-specific immunity, or natural immunity, includes those defences operating in the absence of specific adaptive immune response. Some simple examples are: an unbroken integument, the secretion of antibacterial molecules (lysozyme, fatty acids), normal bacterial flora, ciliary action, mucus production, secretion of tears, saliva and other flushing materials, coughing and sneezing mechanisms. Other components of natural immunity are factors of the inflammatory and phagocytic responses, such as pyogens, certain proteins of the coagulation sequence, 'natural antibodies' found in the serum in the absence of antigenic stimulation, components of the complement systems, phagocytic cells, and various naturally occurring cytotoxic cells. These responses are selective in differentiating self from non-self,

but are not dependant on specific recognition. They represent the initial encounter with foreigners and repeat the same general response with each encounter. (Bellanti 1979:12 and Guyton and Hall 1996:445).

(2) Specific immunity, or acquired immunity, depends on exposure to a foreign molecular configuration and the subsequent recognition of and reaction to it. It is characterised by: (a) specificity, in recognising self from non-self and in reacting solely with the molecular configuration which initiated the response; (b) heterogeneity, in which a vast array of cell types and cell products are induced to interact with a diversity of response; (c) memory, resulting in augmentation of the specific response through proliferation and differentiation of cells upon subsequent exposure to an immunogen. (Bellanti 1979:12 and Guyton 1986:448).

The response of the immune system to an immunogenic stimulus involves an afferent limb and an efferent limb. The afferent limb is the series of cellular events which occur prior to the expression of the specific immune response (they are mostly non-specific). Here macrophages, both circulating and fixed cells, process immunogens, and cellular interactions occur between macrophages and lymphocytes, culminating in the activation of lymphocytes. (Bellanti 1979:12-13).

The efferent limb involves two interacting effector mechanisms: humoral immunity and cell-mediated immunity (Bellanti 1979:13). Humoral immunity is provided mainly by B lymphocytes. They react to extracellular pathogens by becoming plasma cells and secreting various antibodies which neutralise exotoxins and viruses, enhance phagocytosis, activate the complement system, and engage in antibody-dependent cellular cytotoxicity (Bellanti 1979:13). Cell-mediated immunity is provided mainly by T lymphocytes, which can be divided into two groups:

(a) T cells fulfilling effector functions. These are either cytotoxic T cells that are capable of destroying virus-infected cells and tumour cells, or delayed hypersensitivity T cells, that participate in delayed hypersensitivity reactions by producing lymphokines which are factors helping macrophages in certain ways; and

(b) T cells that have regulatory functions. These are either helper T cells that assist the proliferation of cytotoxic T cells and delayed hypersensitivity T cells and the development of B cells into plasma cells; or suppressor T cells that act to curtail the previously mentioned activities. Through these regulatory T cells humoral immunity and cell-mediated immunity merge. (Bellanti 1979:14).

Natural killer (NK) cells comprise 10% to 15% of human peripheral blood lymphocytes (PBL) and most have the morphology of large granular lymphocytes (LGL) (Timonen et al. 1981). NK cells are defined functionally by their ability to lyse target cells without deliberate prior sensitisation and without restriction by major histocompatibility (MHC) antigens (Lanier et al. 1986). NK activity varies substantially among individuals. Within individuals, NK activity tends to be stable over time but measurements of NK activity within a population can define low and high responders, and these levels may be influenced by age, sex, exercise and a variety of general health factors. Circadian variations in NK activity have been demonstrated in humans, with a maximum activity occurring in the morning or early afternoon (Gatti et al. 1987). This makes it important in the serial monitoring of NK activity to obtain each blood specimen at the same time of the day.

The role of NK cells appears to be both important and multifaceted. Today, NK cell activity is widely viewed as an efficient non-MHC-restricted effector cell which is capable of "policing" the host and getting involved in the defensive action against infectious agents, transformed cells, and perhaps certain immature normal cells. It mediates natural and antibody-dependent cytotoxicity (Herberman and Ortaldo 1981). Its contribution to the host defensive system has been well documented and only now scientists are gradually beginning to dissect and understand the

levels of NK cell functions prior to, during, and after a disease process.

> There is also evidence that the NK cell exercises regulatory influences on other components of the immune system and on tissue cells. NK cells, when activated, produce lymphocytes and through the cytokine cascade participate in the immune control network. Because the NK cell appears to be involved in multiple effector, regulatory and developmental steps of the immune system, it's importance in human disease cannot be overemphasized. Some investigators believe that low NK number / low NK activity may be among the most sensitive indicators of biological modulation. (Whiteside and Herberman 1989).

From this overview, the immune system's complexity is evident. Many organs are involved, including the bone marrow, liver, spleen, lymph nodes and lymphoid tissues. Many systems are involved, including the macrophage and reticuloendothelial system, the complement system, the coagulation and vasoactivity system, the humoral immune system and the cell-mediated immune system. All of these are coordinated by a myriad of chemical mediators in fine balance. Therefore, it is biologically plausible, given the pervasiveness and diversity of the immune system, that nerve function might influence immune function. (Allen 1993.)

2.4.1 NEURAL-IMMUNE INTERACTIONS

Demonstration of innervation of lymphoid organs provides indirect though compelling evidence that the neurotransmitter contained in that nerve affects immunocytes. The innervation of blood vessels and the capsule of the spleen, and its role in regulating splenic sequestration of immunocytes, has long been appreciated. The demonstration that in both primary lymphoid organs (such as thymus and bone marrow) the parenchyma is richly innervated, indicates a more direct way by which the nervous system could affect the immune system (Lundberg et al. 1985).

Such innervation has been extensively demonstrated for catecholaminergic neurons, particularly in the studies by Felten et al. (1987) in murine systems. These studies employed antibodies directed against tyrosine hydroxylase to identify adrenergic neurons. Tyrosine hydroxylase is a specific marker for such neurons, and the use of these antibodies circumvents the many technical problems arising when attempting to identify adrenergic nerves based on their catecholamine content. Of great interest are the reports by Felten et al. (1987) of adrenergic neurons ending in close apposition to lymphocytes, apparently forming synapse-like structures. The precise function of these connections is unknown, but they potentially provide an opportunity for lymphocytes to be exposed to high concentrations of neurotransmitters, because concentrations of neurotransmitters three or four orders of magnitude higher than those found in the blood are found in the synaptic cleft.

2.4.2 Neural-immune interactions mediated via lymphocyte receptors

2.4.2.1 Neurotransmitters

2.4.2.1.1 Norepinephrine

The best characterized lymphocyte neurotransmitter receptor is the b2-adrenergic receptor. The number of receptors per cell and their affinity as determined by Scatchard analysis have been relatively consistent in studies from many laboratories. Binding and production of the second-messenger cyclic AMP have shown appropriate specificities with respect to stereo specificity, inhibition with appropriate inhibitors, reversibility (in the case of binding), and rank order of potency (cyclic AMP production).

b2-adrenergic receptors have been detected on B, T- helper, and T-suppressor cells isolated from blood; however, their relative distribution on different cell types, as assessed by binding and cyclic AMP production, is still controversial. Certain cloned T cell lines (derived by antigen stimulation in vitro of lymphocytes obtained from healthy subjects) appear to express this receptor, whereas others (often from the same person) do not. This raises the possibility that cells of different subsets or at distinct stages of activation may differ with respect to receptor expression. (Halper 1991:122).

In contrast to the b-adrenergic receptor, little attention has been given to immunocyte a-adrenergic receptors. In peripheral blood mononuclear cells, there is preliminary evidence that a1 stimulation does not lead to phosphoinositol (PI) turnover (which occurs in other tissues with a receptors); however, this does not preclude such an effect with potential functional significance on minor populations of cells, such as B cells and Natural Killer (NK) cells. Indeed, presumptive evidence has been presented for the existence of a1 and a2 receptors in murine immunocytes based on the functional effect of appropriate agonists and antagonists on antibody formation by spleen cultures *in vitro* (Sanders and Munson, 1985). The uncertainty regarding the importance of a receptors in *vitro* clearly complicates the interpretation of results with the naturally occurring catecholamines, epinephrine, and norepinephrine, which, in contrast to isoproterenol (a relatively pure b- adrenergic agonist), have strong a effects.

Many functional effects of catecholamines on the immune system have been reported in vivo and in vitro, but their interpretation is not straightforward. In vitro effects (which are generally inhibitory) are often seen only at concentration of agonist orders of a magnitude higher than those seen in the plasma. This may reflect the instability of these compounds in vitro or may indicate that cells are affected only in certain locations where concentrations are high. Another potential explanation

for differences between in vivo and in vitro studies are effects resulting from lymphocyte redistribution (which can occur only in *vivo*) or effects on nonlymphoid tissue. Alternatively, meaningful effects may be seen only when lymphocytes are simultaneously exposed to catecholamines in combination with the neuropeptides with which they are co-released (Halper 1991:128).

2.4.2.1.2 Serotonin

The overall effects of serotonin on the immune system are complex, with stimulatory and inhibitory effects being reported. An additional level of complexity is added, because blood has virtually no free serotonin; most intravascular serotonin is contained in platelets. Release of serotonin by these cells occurs in response to participation in immune reactions and during the coagulation process. Platelet release is the source of most of the serotonin at the site of immune reactions in humans. In mice, mast cells also make an important contribution to local serotonin concentrations (Halper 1991:129). It has been reported that systemic administration of serotonin just before immunization decreased antibody synthesis (Jackson et al. 1985). These investigators present compelling evidence that the decrease was mediated directly by peripheral serotonin rather than a central nervous system (CNS) effect (including a centrally mediated increase in corticosteroid). Clear evidence for a direct effect of

serotonin on immunocytes was presented by Sternberg et al. (1986), who reported that increased expression of Ia antigens [which are necessary to 'present' foreign antigens in immunogenic form to T cells in the delayed type hypersensitivity (DTH) and other immune reactions] is induced on macrophages by interferon-g-stimulated macrophage phagocytosis. At low interferon concentrations, serotonin increased phagocytosis, whereas at high interferon concentrations, serotonin diminished it.

2.4.2.1.3 Acetylcholine

The role of acetylcholine in immune function is controversial. Various functional effects of cholinergic agonists, including augmented cytotoxicity and antibody synthesis, have been reported (Halper 1991: 130). The major issue regarding the physiology of cholinergic receptors on immunocytes is the origin of agonist. Because of circulating cholinesterases, acetylcholine is essentially undetectable in blood. Early conclusions that cholinergic nerves were present in lymphoid tissue were based on demonstrations of neuronal staining for acetylcholinesterase; however, the specificity of this putative marker of cholinergic neurons has been challenged. There have been several reports that thymocytes produce a peptide able to bind to muscarinic receptors, suggesting a role for immunocyte production of an endogenous ligand. In addition, lymphocytes might be exposed to acetylcholine while circulating through

those glands with prominent cholinergic innervation and accessibility to lymphocytes (e.g., salivary glands). (Halper 1991:131).

Furthermore, acetylcholine may have indirect immunomodulatory effects through its regulation of circulating catecholamines (Janowsky, et al. 1986).

2.4.3 ENDOCRINE-IMMUNE INTERACTIONS

In addition to autonomic nervous system activity, the immune system is influenced by neuroendocrine outflow from the pituitary. All immunoregulatory processes take place within a neuroendocrine environment that is sensitive to the influence of the individual's perception of and response to events in the external world. Because lymphocytes bear receptors for various hormones and neuropeptides, the cellular interactions that mediate humoral and cellular immune responses can be modulated by the neuroendocrine environment in which these immune responses occur. (Ader et al. 1995).

2.4.3.1 HORMONES

2.4.3.1.1 PROLACTIN AND GROWTH HORMONE

In rodents, deficiencies of growth hormone are associated with abnormal

cellularity of the bone marrow and thymus, together with diminished antibody production, T-cell function, and NK-cell activity. These effects are, to a large extent, overcome by administration of exogenous growth hormone. Prolactin exerts a stimulatory effect on immune function. Inhibition of pituitary prolactin secretion suppresses antibody and cell mediated immune functions and increases susceptibility to infections such as *Listeria monocytogenes.* These defects in immune function can be reversed by exogenous treatment with prolactin or dopamine antagonists given to stimulate endogenous release of prolactin. Prolactin released in response to stressful experiences counters many of the immunosuppressive effects of corticosteroids. (Ader et al. 1995).

2.4.3.1.2 Adrenocorticotropic hormone

Lymphocytes bear receptors for corticotropin-releasing factor (CRF), adrenocorticotropic hormone (ACTH), and endogenous opioids. Endorphins (and enkephalins) directly influence antigen-specific and non-specific in vivo and in vitro responses, the direction and magnitude of the effects being determined by several factors including the nature and quality of the peptides, their binding sites, and the timing of administration in relation to dose and route of antigenic stimulation (Heijnen et al. 1991). Although there are direct immuno-modulatory effects of CRF and ACTH, their major *in vivo* effects are exerted through

interactions with other hormones and immune products (Ader et al. 1995).

The most conspicuous hormonal influences on immune function are achieved through ACTH-induced release of adrenocortical steriods. The administration of glucocorticoids to reduce inflammatory reponses and to prevent rejection of transplanted tissue is based on their immunosuppressive effects. However, many immunosuppressive properties of corticosteroids were observed after pharmacological rather than physiological doses of the hormone. In physiological doses, glucocorticoids are essential for normal immune function (compromised adrenal function increases susceptibility to infections) and, in some circumstances, corticosteroids can be immunoenhancing. (Ader et al. 1995).

The generally immunosuppressive effects of glucocorticoid release may protect the organism against and overreaction of the immune system that could lead to autoimmune disease (Munck et al. 1984). In the case of experimental allergic encephalomyelitis, a central demyelinating autoimmune disease, the anti-inflammatory effects of corticosterone attenuate the time-limited course of the paralysis. However, adrenalectomised animals do not recover from this condition unless treated with glucocorticoids. An apparent defect in the release of CRF and the diminshed adrenocortical activity in Lewis compared with Fisher

strain rats makes the former more susceptible to the induction of rheumatoid arthritis. These findings show the pathophysiological consequences of neuroendocrine-immune system interactions (Ader et al. 1995).

Pathways between the endocrine system and the immune system are also bi-directional. Neural- or lymphocyte-derived cytokines contribute to the interacting feedback mechanisms regulating the hypothalamic-pituitary-adrenal (HPA) axis and its target organs by triggering CRF release or stimulating (e.g. growth hormones) and inhibiting (e.g. prolactin) production of pituitary hormones (Besedovsky et al. 1986; Rettori et al. 1987). The potential interaction between neuroendocrine and immune processes is further shown by observations that immune cells activated by immunogenic stimuli are capable of producing neuropeptides (Ader et al. 1995).

2.4.3.2 NEUROPEPTIDES

Neuropeptides have been the foci of active investigations in neuroimmunolgy as well as in other areas of neurobiology. Many neuropeptides have been shown to be produced by non-neural tissues, including lymphocytes and monocytes. (Halper 1991:134).

2.4.3.2.1 Substance P

Substance P was the first neuropeptide identified as having a role in immune function. Some sub-populations of human T-lymphocytes and other white blood cells contain receptors for the neuropeptide Substance P (Payen and Brewster 1983; Payan and Goetzl 1985). Activation of these receptors has various effects, including proliferation of T-lymphocytes (Payen and Brewster 1983), increased phagocytosis of yeast particles by polymorphonuclear leukocytes (Payen and Goetzl 1985), margination and endothelial adherence of polymorphonuclear leukocytes and monocytes to venules, and degranulation of mast cells causing release of histamine (Goetzl et al. 1985).

Substance P also influences the immune response by acting directly on various tissues. When injected under the skin, Substance P produces a flare, wheal and itching which are only partially blocked by antihistamines. In the gut, Substance P causes smooth muscle contraction and stimulates peristalsis. In the respiratory tract, Substance P causes long-lasting contractions in the trachea and bronchial muscles resulting in increased insufflation pressure (Pernow 1985). When Substance P is given intravenously or as an aerosol, human subjects experience flushing, diaphoresis, rhinorrhea, hypotension, coughing and bronchospasm (Goetzl et al.1985). Substance P is an extremely powerful

vasodilator and smooth muscle contractile factor (Goetzl et al. 1985; Pernow 1985). In human skin, for example, Substance P is approximately 100-400 times more potent than histamine (Goetzl et al. 1985).

As primary afferent neuromodulator, Substance P is transported by axoplasmic flow to the central terminals of C and A delta fibers, where it is released in response to noxious mechanical, thermal and chemical stimuli onto cells in the substantia gelatinosa of the spinal cord (Guyton and Hall 1996:553). It is now clear that these same primary afferent neurons also release Substance P peripherally (Pernow 1985). Up to 90% of the Substance P synthesized by C fibers is transported to the peripheral terminals of the fiber (Levine et al. 1985), and the rate of transport to the periphery has been estimated to be 10 times faster than the rate of transport to the central terminals (Foreman and Jordan 1984). When these fibers are stimulated antidromically, they release Substance P from their peripheral terminals which results in neurogenic inflammation of the tissue supplied by those C fibers (Pernow 1985).

C fibers which contain Substance P represent about 20% of the small diameter dorsal root ganglion neurons (Jessel 1985). Their peripheral terminals are found in the skin, mucous membranes and gastrointestinal tract (Pernow 1985). The sensory portion of the trigeminal nerve, which

supplies the eye, mouth, lips, nasal mucosa and dental pulp, has Substance P containing fibers which are often found directly connected to blood vessels, secretory elements and smooth muscle (Pernow 1985). The visceral primary afferent axons, which travel with the vagus and supply the respiratory tract, also contain Substance P (Pernow 1985). It appears that Substance P released from these vagal afferents may be the second mediator needed for maximum changes in permeability and smooth muscle tone characteristics of immediate sensitivity in the respiratory tract (Goetzl et al. 1985).

It is interesting to note that the effects of Substance P on human tissue are also found as symptoms of allergic disorders such as asthma, allergic rhinitis and atopic dermatitis. Considering the effects of Substance P and its distribution throughout the body, it seems reasonable to speculate that many allergic conditions might be at least partly due to some type of nervous system dysfunction resulting in inappropriate release of Substance P. This mechanism could also be a factor in determining host resistance, given the effects of Substance P on white blood cells. (Fidelibus 1989).

2.4.3.2.2 Vasoactive intestinal peptide (VIP)

The presence of VIP receptors on T-cells has been clearly demonstrated by direct binding studies in murine lymphocytes obtained from spleen and lymph nodes (Ottaway and Greenberg 1984) and human peripheral blood T lymphocytes (Danek et al. 1988).

Elegant studies by Ottaway (1984) have indicated a role for VIP in lymphocyte circulation *in vivo*. Treatment of T-cells obtained from murine mesenteric nodes with concentration of VIP sufficient to down-regulate VIP receptors led to a dose-dependant decrease in their ability to home to Peyer's patches and mesenteric lymph nodes. This contrasted with normal homing to spleen, liver and blood , indicating the potential exquisite specificity of effects mediated by neuropeptide receptors. Although an attractive interpretation of these studies is that the VIP receptor is involved in recognition of vascular signals for recirculation, an alliterative explanation is that the altered circulation pattern resulted from elevations of C-AMP that occur secondary to VIP receptor occupation.

VIP receptors have not been identified on B cells and because VIP fails to affect B cell mitogenesis, the modulation of immunoglobulin synthesis most probably results from an action of VIP on T cell regulation of B cell function rather than from a direct effect on B cells. (Halper 1991:136).

2.4.4 SPINAL MANIPULATION AND IMMUNE FUNCTION

Currently it is not possible to determine whether there are identifiable systemic consequences, including immunologic consequences, of vertebral subluxation.

The demonstration of such cause and effect relationships requires that stringent criteria are satisfied. These criteria include the relative strength of the study designs used to determine causality, the consistency of the association, the temporal sequence of exposure (subluxation) and outcome (systemic effect), and freedom from bias of the diagnosis of a subluxation and the appearance of the presumed outcome. There is no convincing evidence that a vertebral subluxation causes a systemic effect. What is known, is that spinal manipulation, which is used by chiropractors to treat subluxation, elicits some very specific effects, quantifiable by well-defined techniques, on both cells and the concentration of some soluble factors found in the body. These cells and soluble factors are involved in immune responses, but they play other physiologic roles as well. (Brennan et al. 1994).

That spinal manipulation elicits somatovisceral effects is a concept common to both chiropractic and osteopathy (Johnson 1981). Convincing evidence for such effects comes from animal model systems, as noted in the work of Sato and Swenson (1984). They showed that experimental mechanical stimulation of rat spinal cord afferents decreased blood pressure and both adrenal and renal nerve

activity. De Boer et al. (1988), more recently, demonstrated an inhibition of gastrointestinal myoelectric activity (EMG) in conscious rabbits by experimental manipulation of the thoracic spine. In contrast, efforts to demonstrate somatovisceral effects in humans after spinal manipulation have produced conflicting results.

The currently accepted model of neurobiological effects of spinal manipulation can be described by two major conceptual categories that have been created for this purpose: impulse-based and nonimpulse-based mechanisms (Korr: 1979). The term impulse-based applies to phenomena related to reflex behaviours of the spinal neuromere and the central nervous system as they are both sustained and disturbed by motion segment dysfunction. The term nonimpulse based applies to phenomena related to the physical or structural status of nerves, especially with regard to compression of neural structures in and around the vertebral motion segment, and to the behaviour of materials internal to nerve structures, specifically axonal flow. The model interrelates the structural considerations, especially compression effects, on nerve roots and other neural elements located in the intervertebral foramen and the peripheral nerves, with functional considerations involving pain behaviour and sensorimotor reflex patterns governing the behaviour of the motion segment and the locomotor system. Manipulation is hypothesized to produce significant short-term bursts of proprioceptive transmission in the large-caliber myelinated alpha-afferent fibres arising from the spinal joint capsules and ligaments and in the muscle spindles of

the local paraspinal musculature (Korr: 1979). These large-fiber signals are believed to modulate the interneuronal pool via the dorsal spinal ganglion and the substantia gelatinosa and act to 'close the gate' on pain transmission (Wall 1978). Evidence exists that sensorimotor reflex connections are also influenced by manipulation via stimulation of the segmental motor pools (Hoehler and Tobis 1982). These two sets of behaviours would result in a reduction of pain transmission (via inhibition of the ascending pain pathways) and a reduction of muscle hypertonicity (via inhibition of alpha motor-neurons). These are the two most evident clinical effects of manipulation (Beurger 1983 and Wall 1978).

Vora and Bates (1980) measured the effects of generalised mobilising spinal manipulation, twice a week for four weeks, on eight patients with radiographically evident neuromusculoskeletal conditions. A significant increase in circulating B lymphocytes was reported in five of the eight patients, and a significant increase in circulating T lymphocytes was reported in one of the eight patients after manipulation. The small number of patients, the use of generalised spinal manipulation rather than specific chiropractic adjustment, and the limited statistical evaluation of measured parameters (a difference of 50% or greater was apparently arbitrarily chosen as the level of significance) all limit the interpretation of this study in evaluating chiropractic treatment.

Alcorn (1977) measured the effect of chiropractic treatment on the levels of IgA, IgG and IgM antibodies in four patients over a two-week period. Three

reported subjective improvement in their neuromuscular condition and also showed increases in all three antibody levels. The fourth patient reported no progress in neuromuscular condition and showed a decrease in all three antibodies. The very small number of patients and the lack of statistically verifiable data limit this study.

Brennan and Hondras (1989); Brennan et al. (1991); Brennan et al. (1992) have approached the question of systemic responses to spinal manipulation in a number of ways. Brennan and Hondras (1989) studied the ability of polymorphonuclear neutrophils (PMN) from both healthy subjects and patients with low back pain to respond in vitro to a particular challenge after spinal manipulation. They found that PMN isolated from subjects who received spinal manipulation exhibited an elevated respiratory burst when challenged with opsonized zymosan in vitro. This data proved evidence in man that spinal manipulation affects cells involved in inflammatory and immune responses, at least over the short term. The manual methods used in their study were also well controlled and reliable procedures, as reported by them.

Brennan et al. (1991) concluded that the mechanism whereby spinal manipulation exerts a priming effect on peripheral phagocytic cells remains a matter of speculation because it is not clear from their experiments if the force of the manipulation results in sufficient direct release of Substance P (SP) to affect circulating phagocytic cells. Their failure to detect significant differences in

plasma SP levels between manipulated and sham manipulated subjects suggests that it does not. However, the assay they used to detect plasma SP is not sufficiently sensitive to detect differences of at less that of 15 pmol/l. Differences in plasma SP levels greater than 15 pmol/l were detected following manipulation in the second SP experiment. Furthermore, their data suggest that under in vitro conditions, pre-incubation with extremely low doses of SP (10 M) is sufficient to prime PMN for an enhanced respiratory burst.

Brennan et al. (1992) in a follow-up study showed that spinal manipulation primes mononuclear cells for enhanced endotoxin induced Tumor Necrosis Factor (TNF) production. Priming for both biological effects was accompanied by slight but nevertheless significantly elevated levels of the neuroimmunomodulator SP. These data support the notion that spinal manipulation elicits viscerosomatic responses; specifically PMN and mononuclear cells over the short term. The capacity of thoracic spine manipulation to elicit biological effects was clearly demonstrated by the data in both studies.

The proximate priming agent for the enhanced PMN measured by chemiluminescence (CL) reponse and the enhanced ability of mononuclear cells to produce TNF following spinal manipulation remains unclear. Brennan et al. (1992) believe that SP remains the most likely candidate. Both SP and TNF can prime neutrophils for an enhanced respiratory burst. (Brennan et al. 1991). SP

can also stimilate TNF production (Renz et al, 1988).

Brennan et al. (1992) concluded that it is not unreasonable to speculate that a positive feedback loop between TNF, SP and possibily other cytokines such as IL-1, IL-6, gamma interferon or prostaglandins might be involved.

Lohr et al. (1990) measured the number and percent of natural killer cells in thirty seven asymptomatic controls and forty new patients presenting for chiropractic care. Patients, presenting for chiropractic care, showed a significantly lower level in both parameters than the controls.

In a study by Brennan et al. (1994) where the lymphocyte profiles in patients with chronic low back pain which were enrolled in a clinical trial were done, it was found that patients with chronic low back pain of greater than 50 days duration, had a lower percentage of natural killer cells and possibly T-suppressor cells than healthy adults. This study failed to demonstrate dramatic treatment effects over time particularly in the natural killer cell subset. In this study manipulation therapy failed to show a clinically significant effect on either the absolute number or percentage of any lymphocyte subpopulation studied.

In assessing the above results, the following methodological issues must be considered:

(1) Lymphocyte profiles were not the primary outcome in this controlled randomized clinical trial (RCT) of manipulative therapy for chronic low back pain, and medication usage was restricted only if it was intended to relieve the symptoms associated with low back pain. Detailed history of the use of medications such as drugs for depression or drugs with cyclooxygenyse inhibiting activity were not obtained from these patients. Both classes of drugs can influence levels of leukotrienes and prostaglandins and these in turn can either up-regulate of down-regulate the immune system depending on their concentration (Phipps et al. 1991).

(2) A second limitation may be the time frame over which the interventions were administered. All treatment was given over a two week period with a follow-up evaluation two weeks later. In the immune system there is continuous renewal and selection of immunocompetent cells, and the total number of cells is under strict control. In such a dynamic system, it takes time to establish sufficient numbers of new cells to be detected as differences in either percentage or absolute number. They simply may not have treated these patients over a long enough time frame or followed them long enough to detect changes in lymphocyte profiles.

Vernon et al. (1986) attempted to measure the effect of spinal manipulative therapy on plasma β-endorphin levels and have found a

statistically significant increase in β-endorphin levels (8.5% increase), five minutes after a single manipulation in the region of the cervical spine, when compared with a control group. However larger studies with serial sampling and attention to assay method reliabilities are needed to further verify these effects. Vernon et al. (1986) concluded that the pain-relieving effect of manipulation is in part due to a short-term increase in β-endorphin levels.

While the evidence presented so far supports the concept of neuroimmunomodulation, it is also consistent with the hypothesis that the musculoskeletal system can result in immune system dysfunction.

This can be explained using Korr's somatosympathic reflex hypothesis (Korr 1979). According to this author proper sympathetic nervous function is dependant on continuous, accurate sensory input to the central nervous system from the musculoskeletal system. When some type of musculoskeletal dysfunction occurs, the sensory input to the central nervous system is altered which may result in segmental sympathetic hyperactivity. Neurological segmental relationships between somatic and visceral structures determine which segments of the sympathetic nervous system become hyperactive. Those tissues innervated by the hyperactive segment of the sympathetic nervous system are adversely affected through changes in perfusion, metabolism and/or

visceral activity, depending on the specific organ or tissue involved. (Korr 1979).

The following findings are particularly relevant when considering somatosympathetic reflexes as possible causes of immune system dysfunction. They are: (a) lymphoid tissues receive sympathetic innervation, (b) some T-lymphocytes contain catecholamine receptors, and the effects of catecholamines on T-lymphocytes appear to be stimulatory at low concentrations and inhibitory at high concentrations. If somatosympathetic reflexes do occur, they would result in increase release of catecholamines from sympathetic neurons. Therefore, a somatosympathetic reflex involving segments which innervate lymphoid tissues could suppress the immune response by inhibiting T-lymphocytes. (Fidelibus 1989).

One type of musculoskeletal dysfunction that might inhibit the immune system through a somatosympathetic reflex is the spinal fixation. According to the spinal fixation hypothesis, when a spinal fixation occurs it is accompanied by segmental facilitation which results in somatosympathetic reflexes. Correcting the spinal fixation with the use of spinal manipulation should eliminate the somatosympathetic reflexes by normalizing the input to the central nervous system from the musculoskeletal system. (Leach 1994 :316.)

CHAPTER 3

3. MATERIALS AND METHODS

3.1 INTRODUCTION

This chapter deals with the methods employed in data collection, as well as the statistical methods used for the interpretation of the data.

3.2 THE OBJECTIVE

This single blind placebo-controlled study proposed to evaluate the effect of spinal manipulative therapy in chronic mechanical low back pain patients, in terms of the patient's perception, objective clinical findings as well as the cellular component of the immune system, in order to assess the role this treatment plays on the cellular components of the immune system and the management of chronic mechanical low back pain.

3.3 THE DATA

Both experimental and questionnaire designs were methods employed in the process of data collection. The data used in this study was of two kinds: primary and secondary data.

3.3.1 THE PRIMARY DATA

The primary data was obtained directly from the patients and consisted of the following:

- Blood samples, analysed by flow cytometry.
- The patient's pain sensitivity, as determined by an Algometer.
- The patient's lumbar spine range of motion (ROM), as determined by a Goniometer.
- Patients' disability as determined by the Oswestry Back Disability Index (Fairbank et al. 1980).
- The patient's pain perception as determined by the Short- Form McGill Pain Questionnaire (Melzack 1987) and the
- Numerical Pain Rating Scale 101. (Jensen et al. 1986)

The above were used to record the response of the patients in an objective manner. It also included the case history, the physical examination and the

lumbar spine regional examination forms, which are used in the Technikon Natal Chiropractic Day Clinic.

3.3.2 THE SECONDARY DATA

The secondary data included journal articles, published reports and books containing information relevant to the research being conducted.

3.4 RESEARCH METHODOLOGY

3.4.1 Subjects

The sample of 30 subjects entered into the study consisted of patients suffering from chronic mechanical low back pain.

Subjects were recruited by placing advertisements in the Natal Mercury, Berea Mail and Highway mail and the local radio station East Coast Radio, indicating that free treatment would be given to patient's suffering from chronic low back pain, who would be willing to participate in the research programme. Upon a reply, potential patient's had the research programme explained to them and the initial consultation was arranged.

Inclusion criteria:

Only subjects suffering from mechanical low back pain syndrome for more than six months or six episodes of low back pain in the previous year, were selected. The diagnosis of mechanical low back pain was based on the Kirkaldy-Willis model. (Kirkaldy-Willis et al. 1992:121).

Exclusion criteria:

(a) Subjects who exhibited any contra-indications to spinal manipulative therapy.

Gatterman (1990: 67) lists the contra-indications to spinal manipulative therapy. This list includes only those conditions relevant to the low back: atherosclerosis of major blood vessels; abdominal aneurism; tumours (e.g.: lung, thyroid, prostate, breast and bone tumours); bone infections (e.g.: T.B., osteomyelitis); traumatic injuries (e.g.: fractures, instability); arthritis (e.g.: ankylosing spondylitis); psychological disorders (e.g.: malingering); metabolic disorders (e.g.: clotting disorders); neurologic disorders (e.g.: space occupying lesions).

(b) Subjects presenting with hard neurological signs.

(c) Subjects suffering from systemic diseases potentially affecting the musculo-skeletal system.

(d) Subjects younger than eighteen years and older than fifty years were excluded from the study.

(e) Subjects who recently received treatment for low back pain.

3.4.2 Experimental design

A sample size of 30 subjects were screened prior to the treatment, by means of a comprehensive case history, physical examination, lumbar spine and pelvis regional examination and completion of Patient Consent Form on their initial visit, to determine if they complied with the inclusion and exclusion criteria.

The randomisation was done as follows: Fifteen labels were inscribed with the letter E (representing the experimental group) and fifteen with the letter P (representing the placebo group). The labels were folded and placed in a box which was agitated to mix the labels. Five labels were drawn each time to represent groups 1 to 6 as indicated below.

Group 1: EEPEP	Group 4: PPEEP
Group 2: PEPEE	Group 5: EPPPE
Group 3: PEEPE	Group 6: EEPPP

As this was a single blinded study, subjects were not aware of which group they were allocated to.

This resulted in two groups of fifteen subjects each, the experimental group receiving spinal manipulative therapy and the other group receiving placebo treatment. The subjects were not aware which treatment they received.

On the initial visit, subjects were screened for the presence of a lumbar facet syndrome, sacro-iliac syndrome or a combination of these two entities before research treatment commenced. If clinically indicated, the subjects underwent radiographic examination of the lumbar spine and pelvis to exclude any contra-indications to therapy.

Symptomatic joints were identified by motion palpation (Schafer and Faye 1989: 211-216, 256-259) and orthopaedic tests. The orthopaedic tests utilised to diagnose facet syndrome were Kemp's test (Gatterman and Panzer 1990:141) and lumbar facet joint challenge (Gatterman 1990: 49 and 84). Those used to diagnose sacro-iliac syndrome were Patric Faber test (Magee 1992:343) and Gaenslen's test (Magee 1992:319).

According to a study done by Evans (1994:545), palpation was found to be a sufficiently precise technique for the assessment of inter vertebral movement. This was used to ascertain which technique would be utilized to manipulate

patients. Subjects found eligible for inclusion in the study were required to complete an informed consent document and assigned to the experimental or placebo group.

The subjects were instructed to be at the clinic by 7:30 am on the same day of the week as blood samples and analysis could only be done between 7:30 am and 8:30 am. This also ensured that circadian variations of cell types in the blood were minimized. Subjects had to return for treatment once a week, on the same day for three consecutive weeks, and then on the same day in the fifth week for a follow-up consultation. The two week follow-up was to allowed to see if the treatment had any effect over a longer period.

On the first, second, third and follow-up consultations, the subjects were taken to the University of Natal, Medical School where blood samples were collected by means of venipuncture in EDTA vacutainer tubes (Becton, Dickenson, Rutherford) before treatment was given. No treatment was given during the follow-up consultation.

The blood samples were held at room temperature until analysed by the following method:

An Epics Profile II Flow Cytometer using a 14 mw air cooled argon laser was

used. Blood collected at the standard time using EDTA as the anticoagulant was processed within 24 hours of venipuncture. Red cells were then lysed and the white cells fixed and stained with a monoclonal antibody CD 16. This antibody was directly conjugated with a fluorescent dye (phycoerythrin). The staining and fixing were performed with an automated Q-prep system. A sample (100 μl) with a white cell count between 50 and 500 X 10/L was used. The lymphocyte sub population was then gated and analysed.

The final count was determined using the white cell count and differential obtained from a coulter STKS analyser and the T, B and NK cell proportions were obtained from the flow cytometer. (Mullbacher et al. 1984).

After blood samples were collected, the subjects were taken to the Technikon Natal Chiropractic Day Clinic where the Oswestry Back Disibility Index, Short-form McGill Pain Questionnaire, and the Numerical Pain Rating Scale 101 were completed by the subjects. An increase in numerical mean values percent indicated an improvement in disibility as measured by the scores of the Oswestry Back Disibility Index.

Lumbar spine range of motion was measured in flexion, extension, left lateral flexion, right lateral flexion, left rotation and right rotation with a BROM II (Back Range of Motion) instrument, (a product of Performance Attainment Associates, 3600 LaBore Road, Suite 6, St. Paul, MN 55110-4144).

Pain sensitivity was measured using an Algometer over the spinous processes of the lower five lumbar vertebrae and the posterior superior iliac spines. An Algometer may be defined as an apparatus for determining sensitivity to pain caused by pressure. The Algometer used in this study was the model "FDK 20 Force Dial", (made by Wagner Instruments and supplied by Activator Methods Inc.). According to Fischer (1987) the reliability of the assessment of pain by the Algometer has been documented and the reproducibility of results collected by those trained in pressure threshold measurements is sufficient for practical use.

The readings produced by both the Goniometer and Algometer allowed for statistical analysis of the objective data. An increase of the numerical values of the readings indicated an increase range of motion and an increase pain tolerance of the affected area to pressure respectively. Increases were interpreted as positive responses to treatment and therefore could be used to indicate the efficacy of chiropractic management of chronic mechanical low back pain.

The experimental group received spinal manipulative therapy to the fixated lumbar vertebrae and/or sacro-iliac joints. The same area was treated on all four treatments. The specific spinal findings did not influence the treatment received. Any of the following techniques were used depending on what suited the patient best:

- lumbar roll (pisiform-mamillary) (Szaraz 1990: 9.1);
- spinous push/hook (Szaraz 1990: 9.11, 9.12);

- sitting lumbar (Szaraz 1990: 9.4)
- upper sacro-iliac joint (flexed innominate) (Szaraz 1990: 9.2) and
- lower sacro-iliac joint (extended innominate) (Szaraz 1990: 9.3).

Lumbar spinal manipulation was based on palpatory findings of fixated segments in individual patients. Sacro-iliac joint manipulation, i.e. either upper or lower joint techniques, was based on the motion palpation findings of restricted motion.

The control group received placebo treatment. This consisted of attaching the Vacotron unit (Vacotron 436 by Enraf Nonius) over the lumbar area and switching it on for a period of 15 minutes per session, but no current. The outcomes measured were reassessed at each visit.

3.4.3 Methods of data analysis

Data analysis was done according to Gulezian (1979:335). As the sample size per group was small (15), non-parametric tests were used.

(1) Procedure 1:

Eighty-eight Mann-Whitney Unpaired tests were used to compare groups 1 and 2. In order to determine whether there was any significant difference between

the two at the $\alpha = 0.05$ level of significance with respect to forward flexion, extension, right rotation, left rotation, left lateral flexion, right lateral flexion, NRS 101 for the worst pain, Numerical Rating Scale 101 for the least pain, Short-form McGill Pain Questionnaire, Algometer, Oswestry Back Disability Index and the Lymphocyte Profiles.

Hypothesis testing and decision rule:

The null hypothesis (H_0)states that there is no significant difference between the two groups with respect to the variable of interest. The alternative hypothesis (H_1) states that there is a significant difference between the two groups.

$H_0 : \mu_1 = \mu_2$ (No significant difference exist between μ_1 and μ_2)

$H_1 : \mu_1 \neq \mu_2$ (A significant difference exist between μ_1 and μ_2)

$\alpha = 0.05$ = level of significance of test.

Decision rule:

For a two-tailed test, at the $\alpha = 0.05$ level of significance,

Reject H_0 if $P \leq \alpha / 2 = 0{,}025$

Accept H_0 if $P > \alpha / 2 = 0{,}025$

P = the observed significant level of the test.

(2) Procedure 2;

One hundred and thirty two Wilcoxon's Signed Rank Tests were used within Group 1 to find out wether there was any significant improvement between consultations 1 and 2, 1 and 3, 1 and 4 (follow-up), 2 and 3, 2 and 4 and 3 and 4. All tests were done at the $\alpha = 0.05$ level.

Hypothesis testing and decision rule:

The null hypothesis (H_0) states that there is no significant improvement between consultation 1 and 2, 1 and 3, 1 and 4 (follow-up), 2 and 3, 2 and 4, and 3 and 4 within group 1 with respect to the variable of interest. The alternative hypothesis (H_1) states the contrary of what the null hypothesis does.

H_0 : There is no significant improvement.

H_1 : There is a significant improvement.

$\alpha = 0.05$ = level of significance of test.

Decision rule:

For a two-tailed test, at the $\alpha = 0.05$ level of significance,

Reject H_0 if $P \leq \alpha / 2 = 0{,}025$

Accept H_0 if $P > \alpha / 2 = 0{,}025$

P = the observed significant level of the test.

(3) Procedure 3:

Wilcoxon's Signed Rank Test was used within Group 2 to determine whether there was any significant improvement between consultation 1 and 2, 1 and 3, 1 and 4 (follow-up), 2 and 3, 2 and 4 and 3 and 4. All tests were done at the α = 0.05 level.

Hypothesis testing and decision rule:

The null hypothesis (H_0) states that there is no significant improvement between consultation 1 and 2, 1 and 3, 1 and 4 (follow-up), 2 and 3, 2 and 4, and 3 and 4 within group 2 with respect to the variable of interest. The alternative hypothesis (H_1) states the contrary of what the null hypothesis does.

H_0 : There is no significant improvement.

H_1 : There is a significant improvement.

$\alpha = 0.05$ = level of significance of test.

Decision rule:

For a two-tailed test, at the $\alpha = 0.05$ level of significance,

Reject H_0 if $P \leq \alpha / 2 = 0{,}025$

Accept H_0 if $P > \alpha / 2 = 0{,}025$

P = the observed significant level of the test.

(4) Procedure 4:

Summary statistics (mean and standard error) were obtained.

(5) Procedure 5:

Bar charts were constructed to present major findings of the study as a visual summary. Bar charts will be made using the package Lotus 123.

The statistical package STATGRAPHICS version 6 + was used for data entry and analysis.

CHAPTER 4

4. RESULTS

This chapter covers the results obtained from the statistical analysis of the data collected from the:

4.1 Lumbar Spine Ranges of Motion

- Forward Flexion
- Extension
- Left Rotation
- Right Rotation
- Left Lateral Flexion
- Right Lateral Flexion

4.2 Pain sensitivity

- Algometer readings

4.3 Pain intensity

- Numerical Rating Scale 101
- Short-form McGill Pain Questionnaire

4.4 Pain quality

- Oswestry Back Disability Index

4.5 Blood: Full blood count

- Haemoglobin
- White blood cells
- Platelet count
- Absolute count

Lymphocyte profiles

- CD 3 count
- CD 4 count
- CD 8 count
- CD 2 count
- CD 19 count
- CD 56 count
- CD 45 RA count
- CD 29 count

4.6 Demographic data

The results are tabulated to display the mean for each group, the exceedence probability value (p-value) and the large sample test statistic (z-value). These values were compared to the level of significance set at 0.05 for all the tests.

4.1: LUMBAR SPINE RANGES OF MOTION

4.1.1: FORWARD FLEXION

Table 4.1.1(a): **Degrees of forward flexion in the experimental and control groups at each consultation.**

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	44	47	48	45	42	48	46	42
2	55	42	28	50	20	48	28	46
3	46	24	46	23	45	21	46	17
4	34	22	34	28	42	32	43	34
5	21	34	26	33	25	32	25	35
6	26	36	18	32	26	20	24	21
7	26	38	30	32	46	27	25	24
8	28	30	36	29	32	35	36	35
9	19	36	23	41	23	42	13	42
10	23	27	21	21	23	28	25	28
11	26	20	28	20	32	22	30	23
12	33	18	34	27	32	24	32	32
13	53	23	51	25	48	25	48	29
14	38	25	24	31	25	26	32	23
15	12	16	10	22	13	20	13	20
MEAN	**32.3**	**29.2**	**30.5**	**30.6**	**31.6**	**30**	**31.1**	**30.1**
STD DEV	**12.2**	**8.9**	**11**	**8.5**	**10.4**	**9.2**	**10.8**	**8.6**

Graph 4.1.1: **Mean values for forward flexion.**

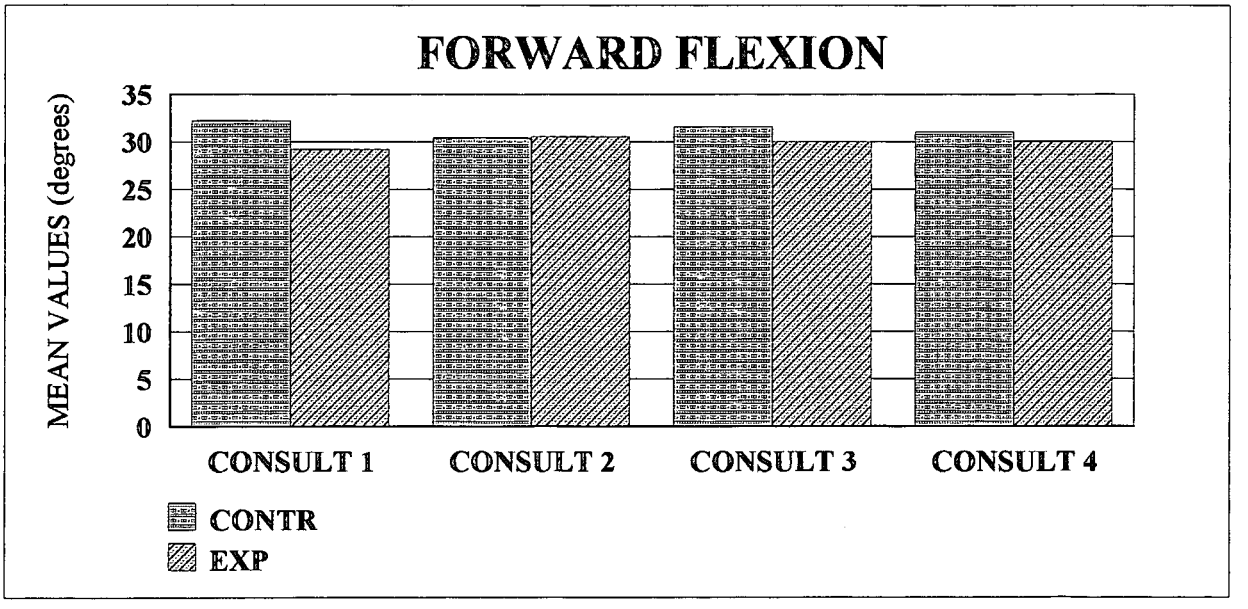

TABLE 4.1.1(b): Wilcoxon's Signed Rank Test for forward flexion.

	CONTROL		EXPERIMENTAL	
	P-values	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	1	0	0.789264	-0.267261
Consult 1 vs Consult 3	1	0	0.789264	-0.267261
Consult 1 vs Consult 4	0.789264	-0.26761	0.301698	1.0328
Consult 2 vs Consult 3	0.789264	-0.26761	0.789264	0.267261
Consult 2 vs Consult 4	0.772826	-0.288675	1	0
Consult 3 vs Consult 4	0.546491	0.603023	1	0

In neither the control, nor the experimental group was there a single statistically significant change at any time in terms of forward flexion. The null hypothesis was therefore accepted.

TABLE 4.1.1(c): Mann-Whitney U-test for forward flexion.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.547193	0.96688	0.723288	0.617962
Z - value	-0.601968	-0.041515	-0.354063	-0.498736

The null hypothesis was accepted for all four Consultations which indicated that at the 5% level of significance no statistically significant difference occurred between the two groups at any time during the study.

4.1.2: EXTENSION

Table 4.1.2(a): **Degrees of extension in the experimental and control groups at each consultation.**

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	12	5	10	27	12	34	12	41
2	20	9	8	14	14	10	12	4
3	5	6	4	4	5	3	6	6
4	11	5	13	6	8	4	7	10
5	4	6	4	13	5	13	5	12
6	6	8	4	8	14	23	10	25
7	6	18	18	8	4	11	19	19
8	8	25	9	35	7	15	6	20
9	7	7	5	5	13	8	11	9
10	2	7	5	10	9	7	2	9
11	24	2	17	2	20	4	16	2
12	22	6	24	6	18	6	18	7
13	14	7	5	7	8	14	8	6
14	14	11	11	18	5	20	11	24
15	2	4	3	15	0	10	3	8
MEAN	**10.5**	**8.4**	**9.3**	**11.9**	**9.5**	**12.1**	**9.7**	**13.5**
MEAN	**6.9**	**8.62667**	**6.1**	**8.8**	**5.4**	**8.1**	**5**	**10.1**

Graph 4.1.2: **Mean values for extension.**

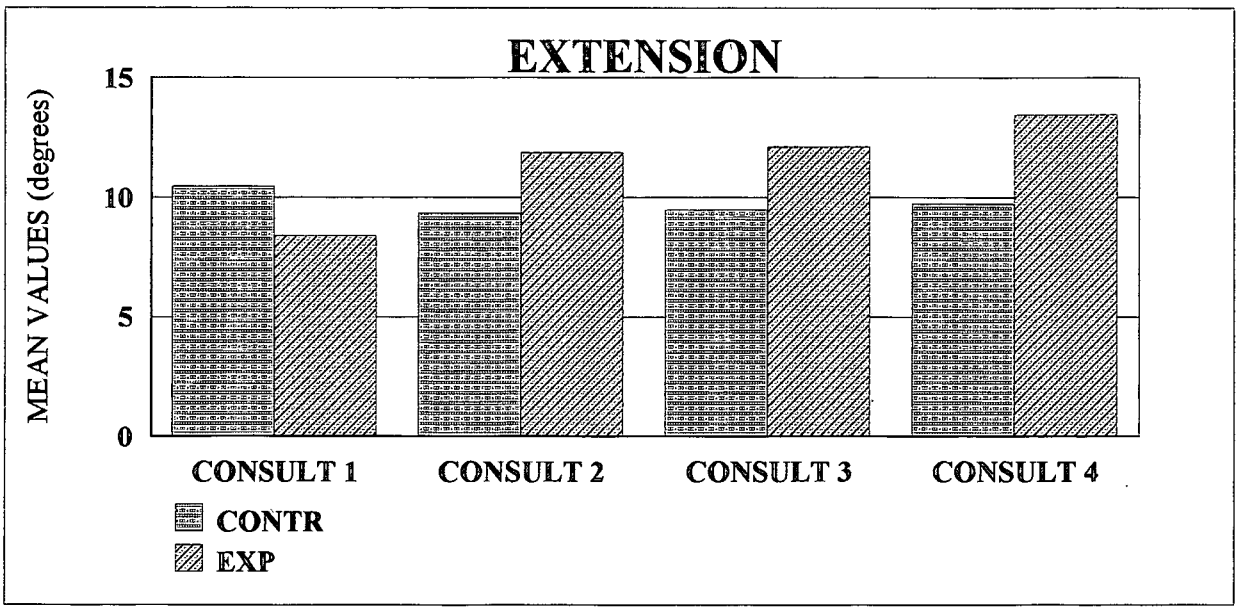

TABLE 4.1.2(b): Wilcoxon's Signed Rank Test for extension.

	CONTROL		EXPERIMENTAL	
	P-values	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	0.789264	-0.267261	0.227799	1.20605
Consult 1 vs Consult 3	0.267256	1.1094	0.267256	1.1094
Consult 1 vs Consult 4	1	0	0.096092	1.6641
Consult 2 vs Consult 3	0.605574	0.516398	1	0
Consult 2 vs Consult 4	0.579097	0.5547	0.789264	-0.267261
Consult 3 vs Consult 4	0.546491	0.603023	0.301698	1.0328

In neither the control, nor the experimental group was there a single statistically significant change at any time in terms of extension. The null hypothesis was therefore accepted.

TABLE 4.1.2(c): Mann-Whitney U-test for extension.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.504916	0.417161	0.519349	0.492715
Z - value	-0.066771	0.811353	0.644345	0.685992

The null hypothesis was accepted for all four Consultations which indicated that at the 5% level of significance no statistically significant difference occurred between the two groups at any time during the study.

4.1.3: LEFT ROTATION

Table 4.1.3(a): **Degrees of left rotation in the experimental and control groups at each consultation.**

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	43	60	58	54	60	58	75	48
2	25	90	55	92	60	50	55	90
3	55	32	59	32	91	48	90	48
4	50	20	55	24	48	50	48	44
5	40	50	50	60	51	63	51	64
6	50	40	60	50	85	52	80	52
7	40	55	40	65	30	61	31	70
8	72	60	55	92	72	75	68	72
9	75	35	40	34	50	35	50	37
10	55	65	50	55	50	60	60	77
11	30	18	30	22	31	30	30	50
12	81	51	81	52	81	60	81	60
13	62	55	60	68	60	72	62	45
14	51	72	30	83	30	90	30	91
15	32	30	30	32	32	30	30	32
MEAN	**50.7**	**48.9**	**50.2**	**54.3**	**55.4**	**55.6**	**56.1**	**58.7**
STD DEV	**16**	**19.2**	**13.6**	**22.2**	**19.5**	**16**	**19.5**	**17.6**

Graph 4.1.3: **Mean values for left rotation.**

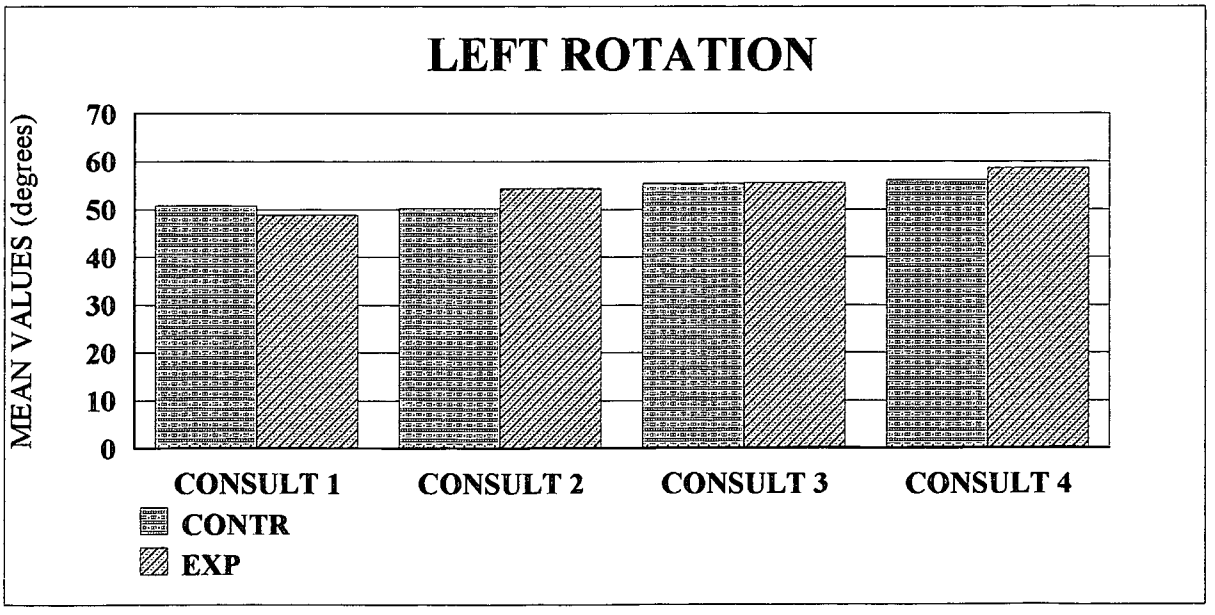

TABLE 4.1.3(b): Wilcoxon's Signed Rank Test for left rotation.

	CONTROL		EXPERIMENTAL	
	P-values	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	0.772826	-0.288675	0.0613685	1.87083
Consult 1 vs Consult 3	0.772826	-0.288675	0.096092	1.6641
Consult 1 vs Consult 4	0.772826	-0.288675	0.0161569	2.40535
Consult 2 vs Consult 3	0.0704401	1.80907	0.1211335	1.54919
Consult 2 vs Consult 4	0.113846	1.58114	0.181449	1.33631
Consult 3 vs Consult 4	0.751826	0.316228	0.386474	0.866025

With the exception of Consultation 1 versus Consultation 4, in the experimental group, no statistically significant change occurred at any time during the study in terms of left rotation.

TABLE 4.1.3(c): Mann-Whitney U-test for left rotation.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.867886	0.6623	0.867607	0.787204
Z - value	-0.166338	0.436736	0.66693	0.269938

The null hypothesis was accepted for all four Consultations which indicated that at the 5% level of significance no statistically significant difference occurred between the two groups at any time during the study.

4.1.4: RIGHT ROTATION

Table 4.1.4(a): **Degrees of right rotation in the experimental and control groups at each consultation.**

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	45	48	63	56	55	51	75	55
2	28	88	53	85	62	58	58	95
3	58	42	60	40	92	42	90	45
4	52	10	58	20	52	40	51	30
5	44	55	50	60	52	60	52	61
6	45	35	70	52	60	52	63	52
7	41	60	38	65	25	62	28	73
8	70	50	61	83	68	85	60	70
9	60	35	45	36	55	36	52	36
10	52	60	48	51	45	60	60	79
11	12	20	10	10	28	28	30	40
12	82	53	83	49	80	55	80	62
13	61	58	61	65	63	70	62	40
14	52	75	25	92	24	87	28	91
15	15	28	16	30	15	30	16	31
MEAN	**47.8**	**47.8**	**49.4**	**52.9**	**51.8**	**54.4**	**53.7**	**57.3**
STD DEV	**18.2**	**19.7**	**19.4**	**22.7**	**20.7**	**17.1**	**20.1**	**20.2**

Graph 4.1.4: **Mean values for right rotation.**

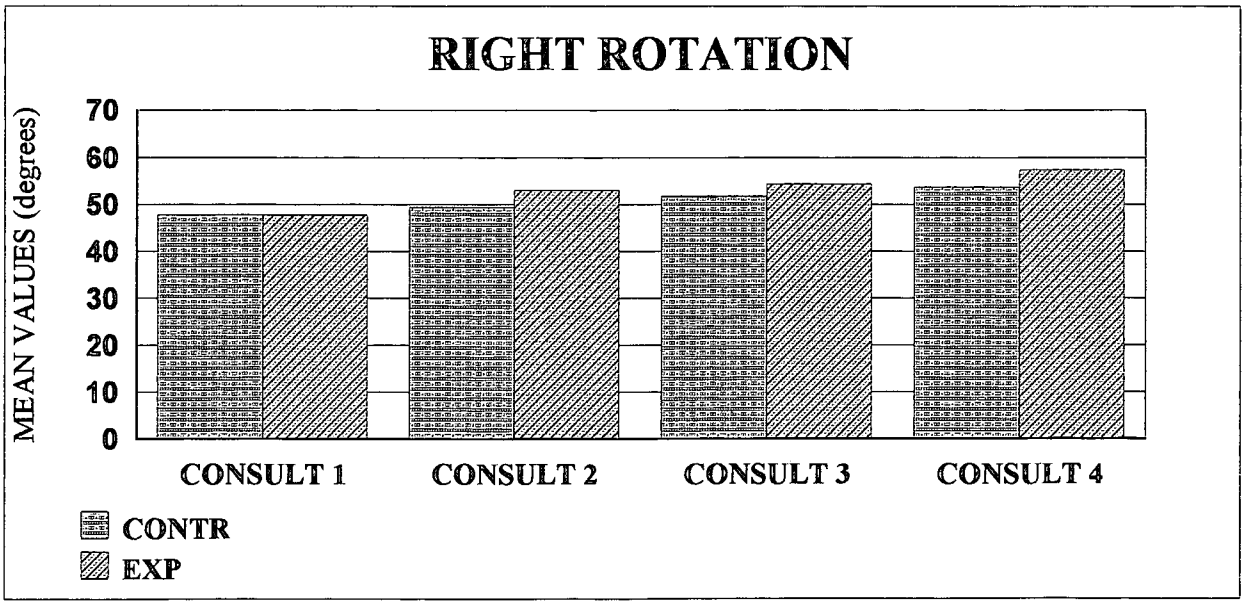

TABLE 4.1.4(b): Wilcoxon's Signed Rank Test for right rotation.

	CONTROL		EXPERIMENTAL	
	P-values	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	0.789264	-0.267261	0.301698	1.0328
Consult 1 vs Consult 3	1	0	0.00554577	2.7735
Consult 1 vs Consult 4	0.605574	0.516398	0.00194591	3.09839
Consult 2 vs Consult 3	1	0	0.546491	0.60323
Consult 2 vs Consult 4	0.422676	0.801784	0.267256	1.1094
Consult 3 vs Consult 4	1	0	0.096092	1.6641

With the exception of Consultation 1 versus Consultation 3 and Consultation 1 versus Consultation 4, in the experimental group, no statistically significant change occurred at any time during the study for right rotation.

TABLE 4.1.4(c): Mann-Whitney U-test for right rotation.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.966865	0.7556	0.835448	0.647872
Z - value	-0.0415335	0.311259	0.207714	0.456716

The null hypothesis was accepted for all four Consultations which indicated that at the 5% level of significance no statistically significant difference occurred between the two groups at any time during the study.

4.1.5: LEFT LATERAL FLEXION

Table 4.1.5(a): **Degrees of left lateral flexion in the experimental and control groups at each consultation.**

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	18	30	30	41	28	30	28	30
2	20	38	32	38	40	23	30	47
3	33	20	33	20	34	30	30	32
4	30	20	30	20	32	20	32	20
5	30	22	40	18	30	28	30	30
6	30	50	30	52	22	30	23	56
7	18	25	18	28	18	25	20	32
8	20	30	15	31	13	40	10	40
9	22	56	18	58	20	56	20	60
10	28	35	22	30	20	33	40	28
11	21	10	18	15	22	22	20	15
12	31	21	31	28	28	25	29	31
13	31	30	30	32	31	40	31	40
14	21	22	20	28	20	32	28	42
15	10	31	10	31	10	30	11	20
MEAN	**24.2**	**29.3**	**25.1**	**31.3**	**24.5**	**30.9**	**25.5**	**34.9**
STD DEV	**6.5**	**11.5**	**8.1**	**11.6**	**7.9**	**8.7**	**7.8**	**12.4**

Graph 4.1.5: **Mean values for left lateral flexion.**

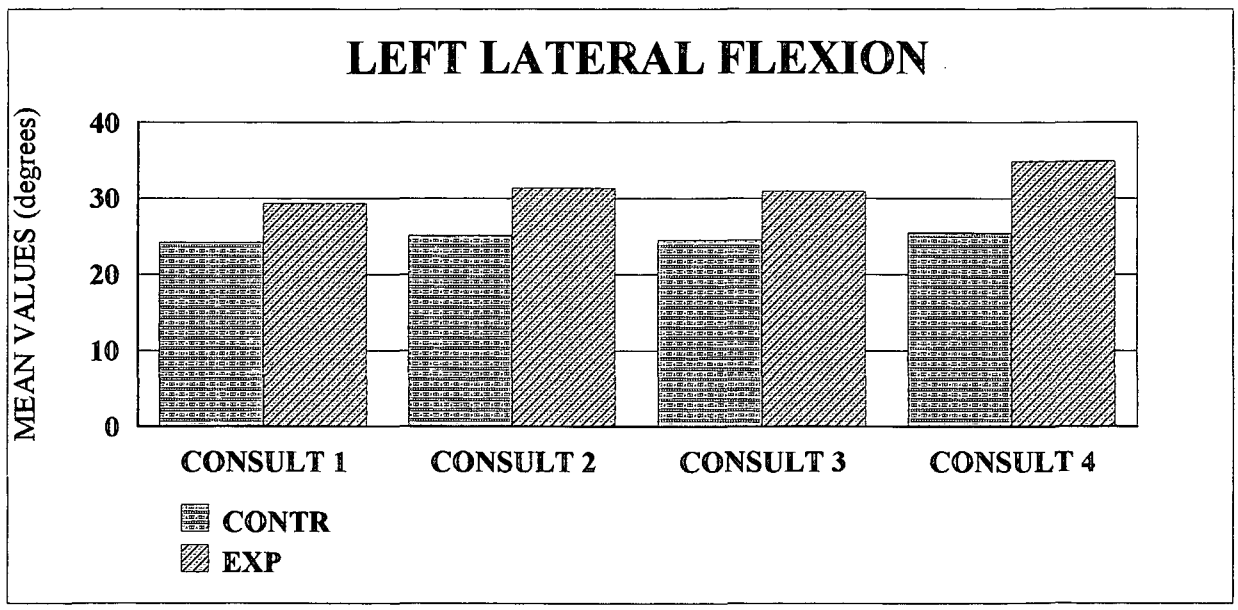

TABLE 4.1.5(b): Wilcoxon's Signed Rank Test for left lateral flexion.

	CONTROL		EXPERIMENTAL	
	P-values	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	0.504983	0.666667	0.0704401	1.80907
Consult 1 vs Consult 3	1	0	0.546491	0.603023
Consult 1 vs Consult 4	1	0	0.0265001	2.2188
Consult 2 vs Consult 3	0.772826	-0.288675	0.789264	-0.267261
Consult 2 vs Consult 4	1	0	0.096092	1.6641
Consult 3 vs Consult 4	0.751826	0.316228	0.227799	1.20605

In neither the control nor the experimental group was there a single statistically significant change at any time during the study in terms of left lateral flexion. The null hypothesis was therefore accepted.

TABLE 4.1.5(c): Mann-Whitney U-test for left lateral flexion.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.225957	0.251682	0.0730762	0.0284841
Z - value	1.21084	1.14627	1.79235	2.19055

The null hypothesis was accepted for all four consultations, which indicated that at the 5% level of significance no statistically significant difference occurred between the two groups at any time during the study.

4.1.6: RIGHT LATERAL FLEXION

Table 4.1.6(a): **Degrees of right lateral flexion in the experimental and control groups at each consultation.**

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	14	40	30	43	30	33	33	35
2	20	50	35	43	39	22	33	49
3	35	25	40	17	38	25	40	30
4	32	18	31	18	32	18	32	20
5	28	30	35	20	28	30	28	30
6	30	60	40	58	25	30	25	60
7	20	20	18	25	17	20	21	28
8	22	33	28	35	25	42	20	35
9	20	51	20	53	21	55	21	63
10	30	28	21	32	20	35	41	30
11	33	20	32	20	28	25	30	25
12	32	20	31	31	30	29	31	33
13	32	35	32	37	31	42	30	40
14	22	22	18	22	19	25	28	38
15	9	30	10	32	10	32	10	22
MEAN	**25.3**	**32.1**	**28.1**	**32.4**	**26.2**	**30.9**	**28.2**	**35.9**
STD DEV	**7.5**	**12.5**	**8.5**	**12.2**	**7.6**	**9.4**	**7.7**	**12.2**

Graph 4.1.6: **Mean values for right lateral flexion.**

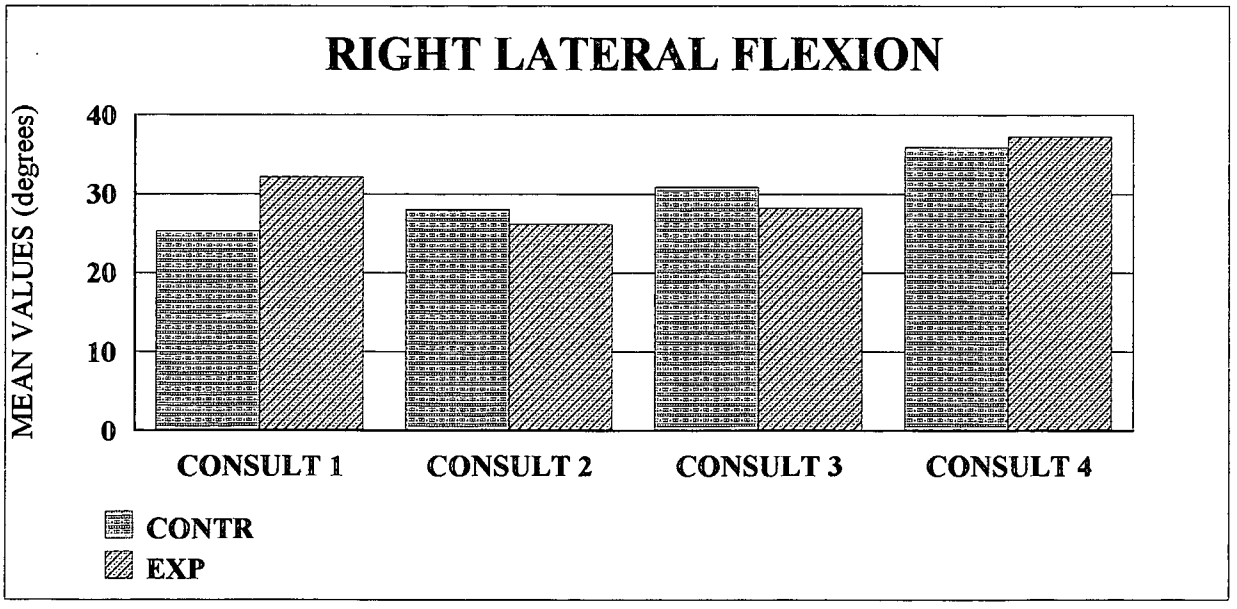

TABLE 4.1.6(b): Wilcoxon's Signed Rank Test for right lateral flexion.

	CONTROL		EXPERIMENTAL	
	P-value	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	1	0	0.386474	0.866025
Consult 1 vs Consult 3	1	0	0.227799	1.20605
Consult 1 vs Consult 4	0.579097	0.5547	0.096092	1.6641
Consult 2 vs Consult 3	0.267256	1.1094	0.579097	0.5547
Consult 2 vs Consult 4	0.772826	-0.288675	0.0613685	1.87083
Consult 3 vs Consult 4	0.34278	0.948683	0.267256	1.1094

In neither the control, nor the experimental group was there a single statistically significant change at any time in terms of right lateral flexion. The null hypothesis was therefore accepted.

TABLE 4.1.6(c): Mann-Whitney U-test for right lateral flexion.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.277827	0.405318	0.243693	0.128627
Z - value	1.08521	0.832157	1.1658	1.51954

The null hypothesis was accepted for all four the Consultations which indicated that at the 5% level of significance no statistically significant difference occurred between the two groups at any time during the study.

4.2: PAIN SENSITIVITY

4.2.1: ALGOMETRIC READINGS

Table 4.2.1: **Algometric readings in the experimental and control groups at each consultation.**

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	6.6	3.7	6.3	4.7	6.7	4.3	6.8	6.3
2	2.5	5.7	3.3	4.6	3.4	6.2	6.7	4.3
3	5.3	5.8	5.8	5.5	4.9	4.2	4.5	4.6
4	3.7	4.8	3.8	5	4	10.3	8.6	8.8
5	11.4	4.8	12	5	13	8	11	8
6	1.5	2.2	4.4	3.7	3.2	5.7	3.2	5.7
7	2	8.8	1.1	8.9	0.7	9.5	0.5	12
8	2.5	2.3	3.2	6	3.3	13	3	13
9	4.2	4.2	4.8	4.8	4.8	5.2	4.8	7.2
10	3	7.5	2.5	3.2	3.8	5.5	3.1	8.2
11	5.8	6.5	5.6	6.7	5.5	6.3	5.6	6.7
12	4	6.7	4	6.3	4.2	6.8	4.5	7.2
13	4	5.2	4	5.2	4	4.8	4.2	3.8
14	1.1	4.3	0.8	5.2	1.7	6.8	1.8	6.8
15	3	3.8	2.5	3.9	2.5	3.8	2.8	2.5
MEAN	**4**	**5.1**	**4.2**	**5.2**	**4.4**	**6.7**	**4.7**	7
STD DEV	**2.5**	**1.8**	**2.6**	**1.3**	**2.7**	**2.5**	**2.6**	**2.7**

Graph 4.2.1: **Mean values for Algometric readings.**

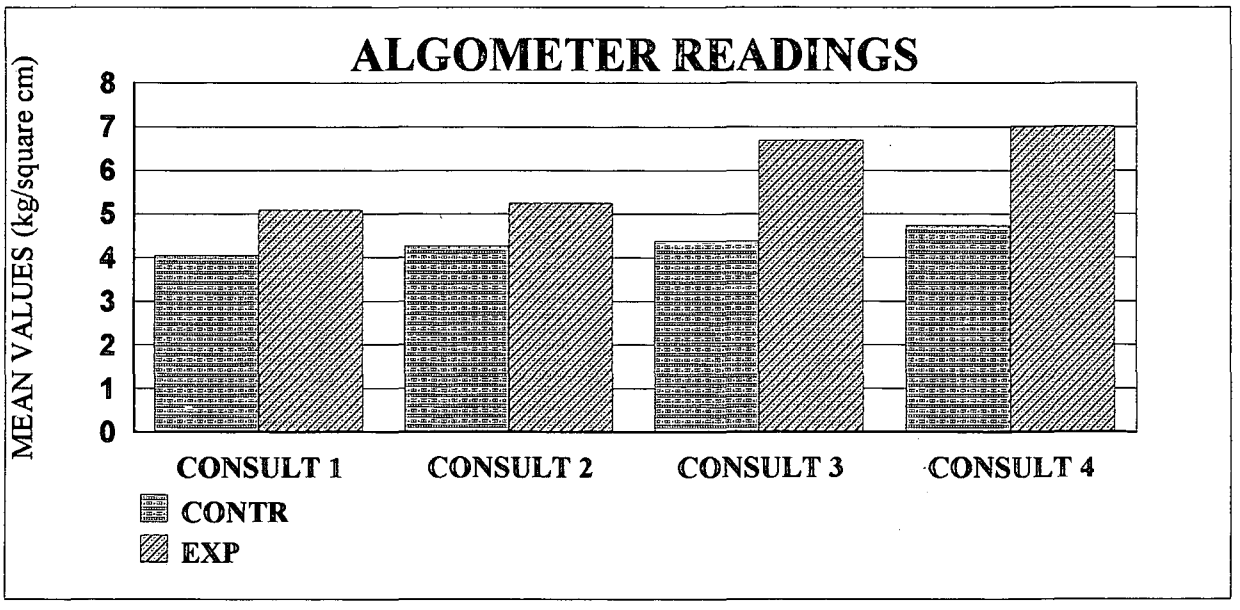

TABLE 4.2.1(b): Wilcoxon's Signed Rank Test for the Algometric readings.

	CONTROL		EXPERIMENTAL	
	P-values	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	1	0	0.181449	1.33631
Consult 1 vs Consult 3	0.181449	1.33631	0.181449	1.33631
Consult 1 vs Consult 4	0.301698	1.0328	0.301698	1.0328
Consult 2 vs Consult 3	0.386474	0.866025	0.301698	1.0328
Consult 2 vs Consult 4	0.579097	0.5547	0.181449	1.33631
Consult 3 vs Consult 4	0.579097	0.5547	0.546491	0.603023

In neither the control, nor the experimental group was there a single statistically significant change at any time in terms of the Algometric readings. The null hypothesis was therefore accepted.

TABLE 4.2.1(c): Mann-Whitney U-test for the Algometric readings.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.0776993	0.064716	0.00299763	0.0278553
Z- value	1.76419	1.84721	2.96799	2.19932

Although a comparison of Consultation 1, Consultation 2 and Consultation 4 showed no statistically significant differences, there was a statistically significant difference between the two groups at Consultation 3.

4.3: PAIN PERCEPTION

4.3.1: NUMERICAL PAIN RATING SCALE 101

Table 4.3.1(a): Numerical Pain Rating Scale 101 values in the experimental and control groups at each consultation.

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	55	50	50	45	50	40	45	15
2	50	35	35	10	20	10	20	0
3	45	50	45	50	20	50	35	30
4	50	40	50	35	10	30	50	47.5
5	0	45	30	45	0	45	0	45
6	50	42.5	50	42.5	0	42.5	0	37.5
7	52.5	0	2.5	0	40	0	40	0
8	9	50	6	0	1	0	5	0
9	25	40	5	40	0	35	0	15
10	45	15	40	40	35	52.5	30	0
11	2.5	85	2.5	85	2.5	70	2.5	70
12	30	22.5	42.5	50	37.5	25	20	15
13	35	15	35	30	37.5	30	30	25
14	45	25	45	27.5	40	12.5	35	17.5
15	65	45	35	45	30	30	60	55
MEAN	**37.3**	**37.3**	**31.6**	**36.3**	**21.6**	**31.5**	**24.9**	**24.9**
STD DEV	**19.3**	**19.5**	**17.6**	**20.8**	**17.5**	**19.2**	**19.2**	**21.4**

Graph 4.3.1: Mean values for Numerical Pain Rating Scale 101

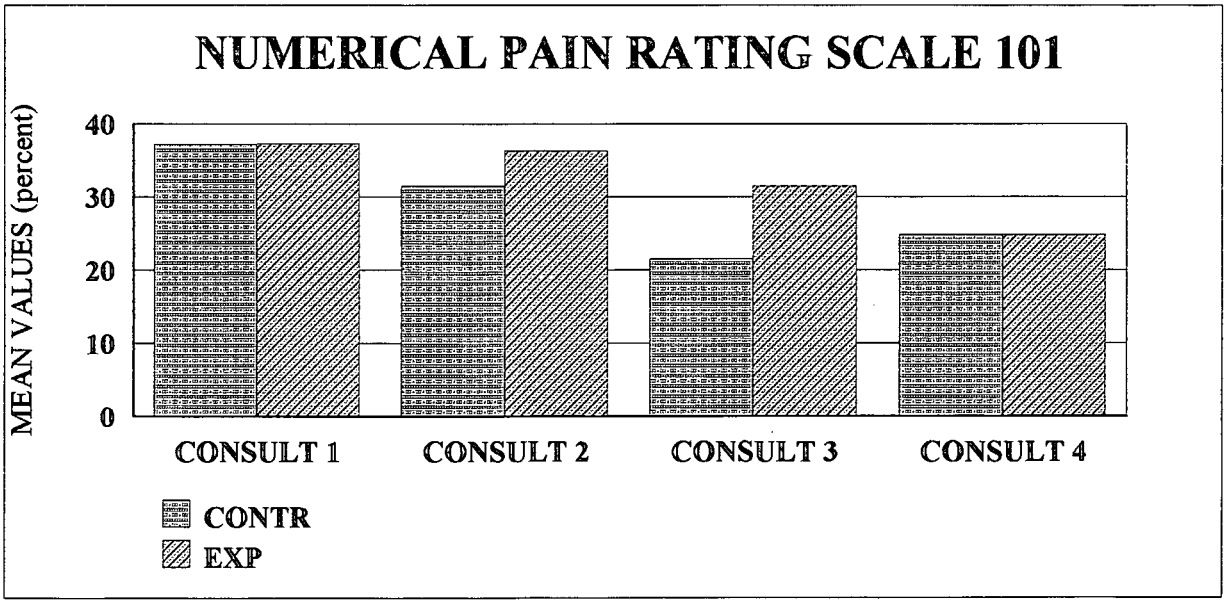

TABLE 4.3.1(b): Wilcoxon's Signed Ranked Test for the Numerical Pain Rating Scale 101 (NRS 101).

	CONTROL		EXPERIMENTAL	
	P-values	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	0.182422	1.33333	0.72367	-0.353553
Consult 1 vs Consult 3	0.0265001	2.2188	0.227799	1.20605
Consult 1 vs Consult 4	0.00149629	3.17543	0.096092	1.6641
Consult 2 vs Consult 3	0.0265001	0.21888	0.0770995	1.76777
Consult 2 vs Consult 4	0.0265001	0.21888	0.0433079	2.02073
Consult 3 vs Consult 4	0.1	0	0.227799	1.20605

With the exception of Consultation 1 versus Consultation 4, in the control group, no statistically significant change occurred at any time during the study in terms of left rotation.

TABLE 4.3.1(c): Mann-Whitney U-test for the NRS 101.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.558809	0.754192	0.211381	0.818205
Z - value	-0.584608	0.313112	1.24978	-0.229849

The null hypothesis was accepted for all four consultations indicating that at the 5% level of significance no statistically significant difference occurred between the control and experimental group, at any time during the treatment period.

4.3.2: SHORT-FORM McGILL PAIN QUESTIONNAIRE

Table 4.3.2(a): Short-form McGill Pain Questionnaire values in the experimental and control groups at each consultation

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	39.74	17.06	55.01	14.32	21.38	12.99	5.52	11.36
2	26.54	24.56	7.57	2.74	8.72	2.74	8.72	0
3	10.89	35.13	5.93	35.13	2.94	35.13	2.94	30.63
4	2.78	29.29	2.78	8.42	0	2.74	0	5.97
5	0	19.89	8.4	20.98	0	30.17	0	17.22
6	28.13	6.96	29.29	12.99	0	13.33	0	8.72
7	15.26	2.96	6.03	2.96	5.87	2.96	2.97	0
8	9.21	57.39	9.21	3.8	0	9.2	6.47	5.8
9	9.93	8.67	16.91	4.44	0	2.96	2.96	1.48
10	17.01	4.26	5.52	8.42	5.75	52.5	5.52	0
11	2.78	70.88	4.26	59.66	4.26	21.5	2.7	64.39
12	19.02	14.98	5.96	2.78	5.76	0	3.78	0
13	8.77	30.67	5.76	18.62	9.11	17.83	5.76	19.19
14	21.14	5.79	17.24	2.78	5.51	2.78	5.51	2.78
15	27.34	29.29	10.53	8.45	7.95	9.43	17.27	11.43
MEAN	**15.9**	**23.9**	**12.7**	**13.8**	**5.2**	**14.4**	**4.7**	**12**
STD DEV	**10.8**	**19**	**13.1**	**15**	**5.4**	**14.4**	**4.2**	**16.4**

Graph 4.3.2: Mean values for the Short-form McGill Pain Questionnaire.

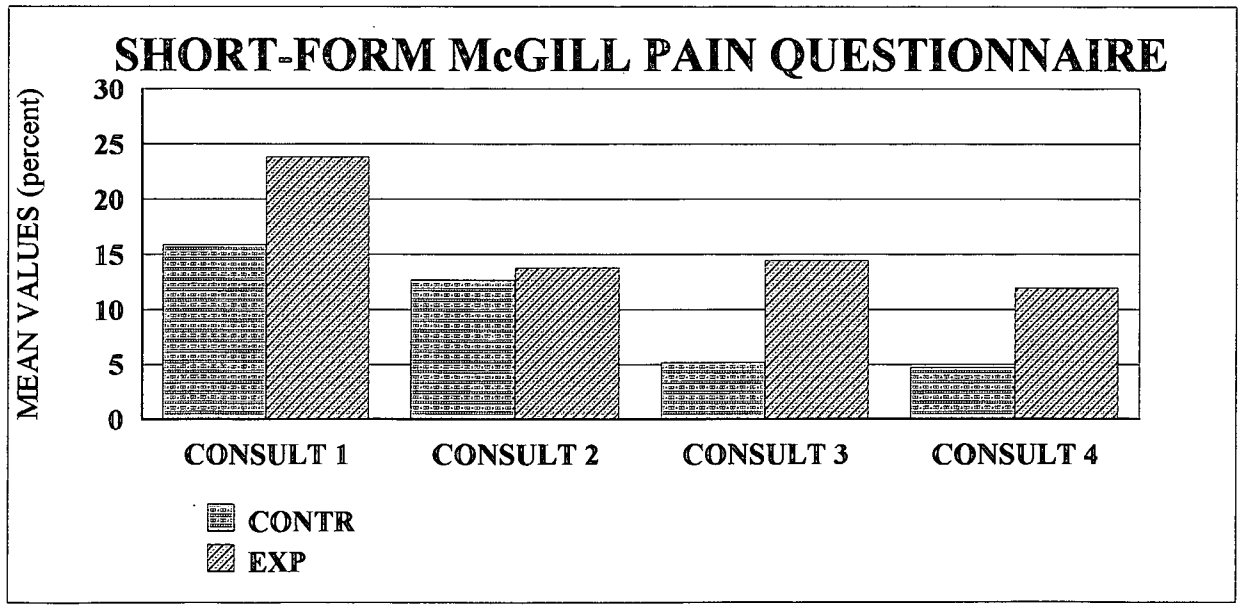

TABLE 4.3.2(b): Wilcoxon's Signed Rank Test for the Short-form McGill Pain Questionnaire.

	CONTROL		EXPERIMENTAL	
	P-values	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	0.579097	0.5547	0.096092	1.6641
Consult 1 vs Consult 3	0.0161564	2.40535	0.096092	1.6641
Consult 1 vs Consult 4	0.00512096	3.4744	0.00194591	3.09839
Consult 2 vs Consult 3	0.0613685	1.87083	1	0
Consult 2 vs Consult 4	0.0265001	2.2188	0.181449	1.33631
Consult 3 vs Consult 4	0.504983	0.666667	0.267256	1.1094

There was a statistically significant change in the control group between Consultation 1 versus Consultation 3 and between Consultation 1 versus Consultation 4. In the experimental group there was a statistically significant change between Consultation 1 versus Consultation 4 at any time during the study.

TABLE 4.3.2(c): Mann-Whitney U-test for the Short-form McGill Pain Questionnaire.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.29965	0.900912	0.0527796	0.306886
Z - value	1.03718	-0.124503	1.93672	1.02283

The null hypothesis was accepted for all four consultations, indicating that at the 5% significance level no statistically significant difference occurred between the two groups, at any time during the treatment period.

4.4: DISABILITY

4.4.1: OSWESTRY BACK DISABILITY INDEX

Table 4.4.1(a): **Oswestry Back Disability Index values in the experimental and control groups at each consultation.**

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	86	82.2	88	88.9	90	93.3	92	95.6
2	88.9	82	86.7	98	88.9	86	88.9	100
3	94	60	90	70	96	56	94	76
4	88	78	88	78	86	82	86	84
5	100	78	100	90	100	82	92	88
6	82	84	83	94	86	90	86	94
7	66	88	68	84	64	86	72	86
8	84	90	72	94	92	96	94	100
9	94	90	86	90	100	90	90	92
10	70	82	80	84	86	70	84	84.4
11	98	64	94	82	94	88	98	88
12	80	92	84	92	96	96	98	98
13	72	68.9	94	75.5	90	91.11	98	91.11
14	86	88	88	88	90	88	92	90
15	30	82.5	44	72.5	50	87.5	30	72.5
MEAN	**81.3**	**80.7**	**83.1**	**85.4**	**87.3**	**85.5**	**86.3**	**89.3**
STD DEV	**16.7**	**9.3**	**13.1**	**8.1**	**12.9**	**10**	**16.4**	**7.8**

Graph 4.4.1: **Mean values for the Oswestry Back Disability Index.**

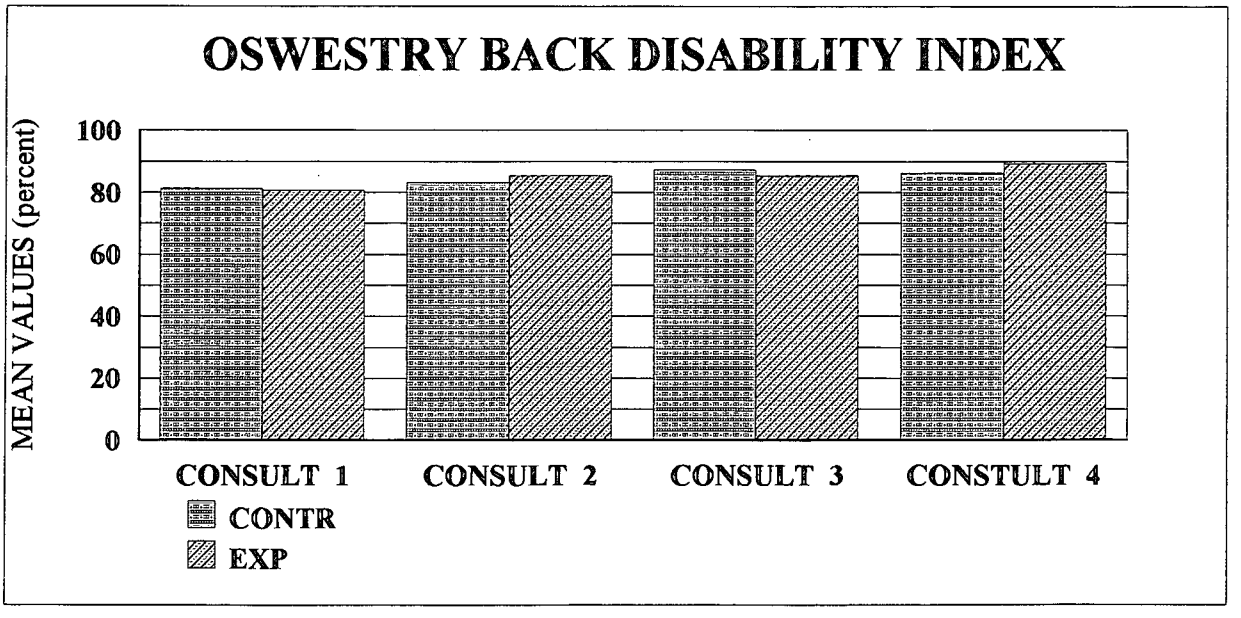

TABLE 4.4.1(b): Wilcoxon's Signed Rank Test for the Oswestry Back Disability Index.

	CONTROL		EXPERIMENTAL	
	P-values	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	0.579097	0.5547	0.0704401	1.80907
Consult 1 vs Consult 3	0.096092	1.6641	0.096092	1.6641
Consult 1 vs Consult 4	0.227799	1.20605	0.00982331	2.58199
Consult 2 vs Consult 3	0.096092	1.6641	0.579097	0.5547
Consult 2 vs Consult 4	0.388669	2.06559	0.00554577	2.7735
Consult 3 vs Consult 4	0.772826	288675	0.00967481	2.59808

With the exception of Consultation 1 versus Consultation 2, Consultation 1 versus Consultation 3 and Consultation 2 versus Consultation 3, statistically significant changes occurred in terms of the Oswestry Back Disability Index in the experimental group.

TABLE 4.4.1(c): Mann-Whitney U-test for the Oswestry Back Disability Index.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.442214	0.723585	0.296892	1
Z - value	-0.768456	0.353667	-1.04312	0

The null hypothesis was accepted at all four Consultations which indicated that at the 5% level of significance no statistically significant difference occurred between the two groups at any time during the treatment period.

4.5.1: HAEMOGLOBIN LEVELS

Table 4.5.1(a): Haemoglobin levels (g/dL) in the experimental and control groups at each consultation.

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	12.4	14.2	12.5	14.5	12.3	14.4	12.7	14.6
2	13.9	15.9	13.8	16	13.9	12.8	12.8	16
3	12.8	14.5	12.2	14.7	12.8	15	12.2	14.5
4	12.8	14.8	12.6	14.9	13.3	15.2	12.8	14.8
5	16	15.2	15.9	15.8	16.1	15.3	15.4	15.2
6	13.4	10.9	13.1	10.6	13.5	10.3	13	10.4
7	13.7	14.6	13.7	14.8	14.3	14.8	13.6	14.3
8	11.7	14.8	11.2	15.4	11.7	15.6	10.5	15.1
9	11.7	12.6	11.8	12	11.5	12.5	12.1	12.8
10	13.3	14.9	13.7	14.9	12.6	15	13.8	14.7
11	14	13.5	14.6	13.1	14.8	13.7	14.8	12.9
12	11.8	14	11.6	15.2	11.8	14.32	12.8	15.2
13	12.4	15	12.4	14.8	12.3	14.8	12.4	14.6
14	11.6	14.8	11.2	15.6	11.7	14.3	12	15.1
15	14.8	15.8	15.1	15.8	14.7	15.9	14.7	15.1
MEAN	**13.1**	**14.4**	**13**	**14.5**	**13.2**	**14.3**	**13**	**14.4**
STD DEV	**1.2**	**1.2**	**1.4**	**1.5**	**1.3**	**1.4**	**1.2**	**1.3**

Graph 4.5.1: Mean values for haemoglobin levels.

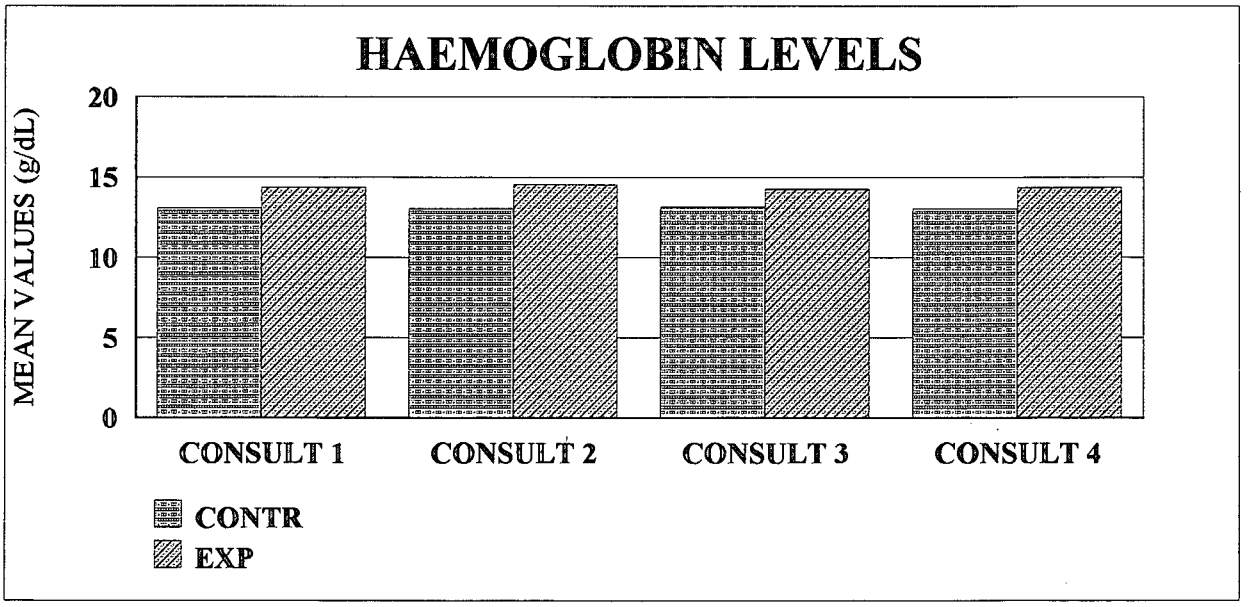

TABLE 4.5.1(b): Wilcoxon's Signed Rank Test for the Haemoglobin levels.

	CONTROL		EXPERIMENTAL	
	P-values	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	0.579097	0.5547	0.267256	1.1094
Consult 1 vs Consult 3	1	0	0.301698	1.0328
Consult 1 vs Consult 4	1	0	0.772826	-0.288675
Consult 2 vs Consult 3	0.301698	1.0328	1	0
Consult 2 vs Consult 4	1	0	0.0265001	2.2188
Consult 3 vs Consult 4	1	0	0.605574	0.516398

In neither the control nor the experimental group was there a single statistically significant change at any time in terms of haemoglobin levels. The null hypothesis was therefore accepted.

TABLE 4.5.1(c): Mann-Whitney U-test for the Haemoglobin levels.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.00692814	0.0120356	0.0179513	0.00938822
Z- value	2.70028	2.5111	2.36662	2.59759

The null hypothesis was rejected for all four Consultations which indicated that at the 5% level of significance, a statistically significant difference occurred between the two groups at any time during the treatment period.

4.5.2: WHITE BLOOD CELL COUNT

Table 4.5.2(a): **White blood cell count (cells/microliter) in the experimental and control groups at each consultation.**

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	8.9	5.8	7.9	9.1	7.6	7.4	6.5	7.7
2	9.4	7.1	9.2	6.7	9.8	8.9	9.1	7.2
3	5.5	14	5.8	14.7	7	12.5	5.8	10.7
4	8.6	8.7	8.9	8.7	8.9	9	8.9	10.4
5	7.6	10.1	7.2	9.6	7.4	8.4	7.2	7.5
6	7.2	8.2	7.4	8.1	8.9	7	6.4	6.6
7	8.8	6.8	8.9	7.5	8.1	6	9.6	5.1
8	9.3	8.5	9.5	8.5	8.8	9.2	9.4	8.8
9	4.1	10.5	3.6	8.6	3.2	8.6	4.1	9.3
10	9.1	5.8	7.1	6.8	8.3	5.9	8.2	5.8
11	5.5	8.7	11.3	10.5	6.9	9.6	5.3	8.4
12	6.4	5.5	8.5	5.3	7	4.6	5.1	6
13	4.4	10	4.7	8.5	6	8.6	8.1	8.3
14	7.6	4.4	7.8	4.2	7.8	4.6	6.8	4.8
15	6.3	6	6.4	5.9	5.5	5.6	12.5	5.3
MEAN	**7.2**	**8**	**7.6**	**8.2**	**7.4**	**7.7**	**7.5**	**7.5**
STD DEV	**1.7**	**2.4**	**1.9**	**2.4**	**1.6**	**2.1**	**2.1**	**1.8**

Graph 4.5.2: **Mean values for white blood cell count.**

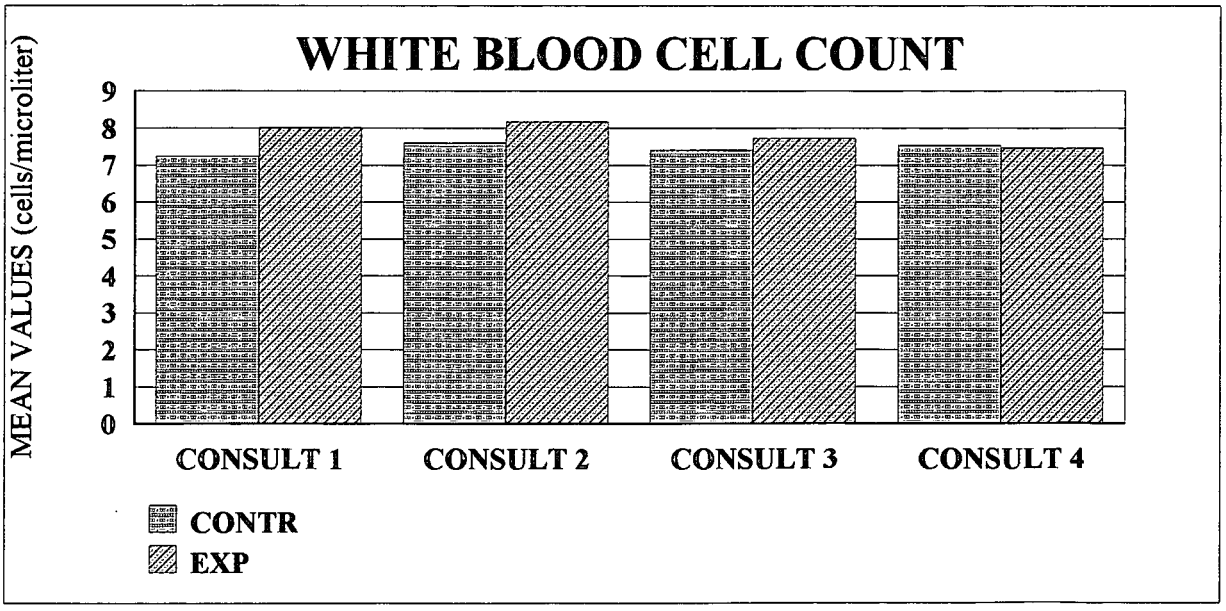

TABLE 4.5.2(b): Wilcoxon's Signed Rank Test for the White blood cell count.

	CONTROL		EXPERIMENTAL	
	P-values	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	0.301698	1.0328	0.579097	0.5547
Consult 1 vs Consult 3	1	0	1	0
Consult 1 vs Consult 4	0.789264	0.267261	0.789264	0.267261
Consult 2 vs Consult 3	1	0	0.422676	0.801784
Consult 2 vs Consult 4	0.772826	0.288675	0.605574	0.516398
Consult 3 vs Consult 4	0.422676	0.801784	0.301698	1.0328

In neither the control nor the experimental group was there a single statistically significant change at any time in terms of white blood cell count. The null hypothesis was therefore accepted.

TABLE 4.5.2(c): Mann-Whitney U-test for the White blood cell count.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.515168	0.648018	0.677893	1
Z- value	0.560453	0.456513	0.415335	0

The null hypothesis was accepted for all four the Consultations which indicated that at the 5% level of significance no statistically significant difference occurred between the two groups at any time during the treatment period.

4.5.3: PLATELET COUNT

Table 4.5.3(a): Platelet count (no/cubic mm blood) in the experimental and control groups at each consultation.

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	257	299	251	305	245	273	238	245
2	296	178	295	177	298	296	349	189
3	248	289	256	358	257	299	250	287
4	251	397	265	417	288	431	296	405
5	254	238	236	248	262	242	267	245
6	329	347	327	371	309	336	285	261
7	278	163	257	144	264	154	246	176
8	220	170	232	182	225	176	254	186
9	282	277	240	231	245	240	234	235
10	313	195	269	206	220	192	330	180
11	201	336	205	275	232	276	193	272
12	294	239	278	244	273	210	243	250
13	238	228	238	230	233	269	308	222
14	284	176	264	148	257	145	283	167
15	175	290	175	270	160	281	200	288
MEAN	**261.3**	**254.8**	**252.5**	**253.7**	**251.2**	**254.7**	**265.1**	**240.5**
STD DEV	**40.4**	**69.6**	**34.6**	**78.5**	**35.1**	**72**	**42.5**	**59**

Graph 4.5.3: Mean values for platelet count.

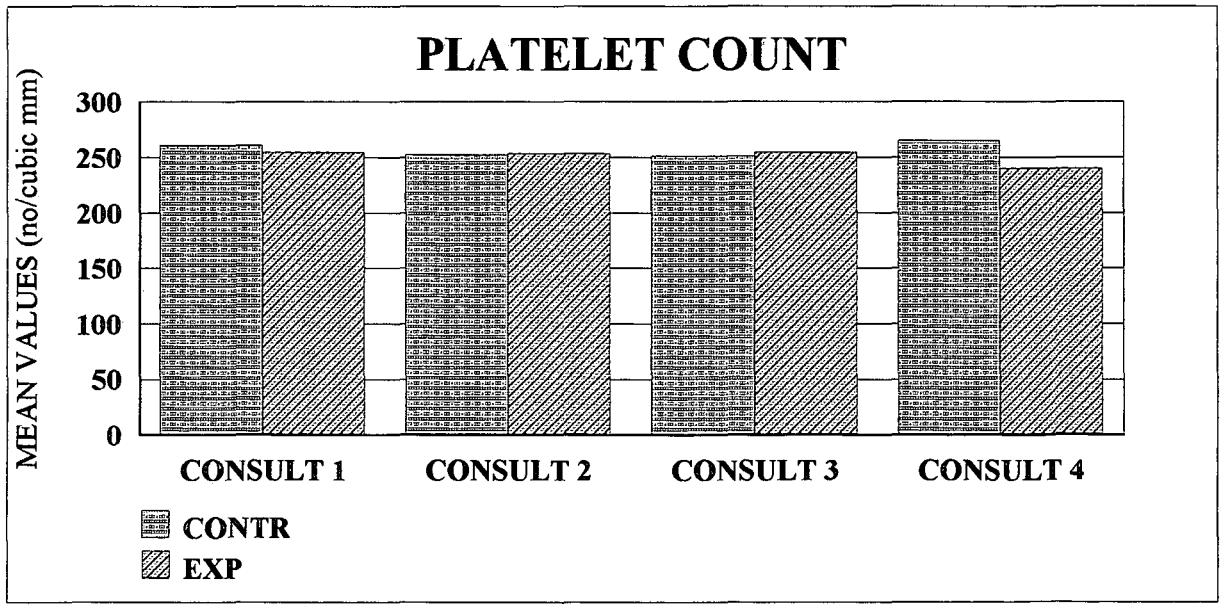

TABLE 4.5.3(b): Wilcoxon's Signed Rank Test for the Platelet count.

	CONTROL		EXPERIMENTAL	
	P-values	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	0.267256	1.1094	0.605574	0.516398
Consult 1 vs Consult 3	0.605574	0.516398	0.605574	0.516398
Consult 1 vs Consult 4	1	0	0.605574	0.516398
Consult 2 vs Consult 3	1	0	1	0
Consult 2 vs Consult 4	1	0	1	0
Consult 3 vs Consult 4	1	0	0.605574	0.516398

In neither the control nor the experimental group was there a single statistically significant change at any time in terms of platelet count. The null hypothesis was therefore accepted.

TABLE 4.5.3(c): Mann-Whitney U-test for the Platelet count.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.663147	0.70892	0.884531	0.129953
Z- value	-0.435568	-0.373303	0.145222	-1.51429

The null hypothesis was accepted for all four the Consultations which indicated that at the 5% level of significance no statistically significant difference occurred between the two groups at any time during the treatment period.

4.5.4: ABSOLUTE COUNT

Table 4.5.4(a): **Absolute count (cells/microliter) in the experimental and control groups at each consultation.**

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	2759	1508	2496	2093	1954	1850	1690	1309
2	2973	2059	2852	2345	2156	2314	2093	2376
3	1045	4900	1914	5292	2030	4250	1740	4194.4
4	2322	3045	2492	2650	2225	2250	2314	3265.6
5	2667.6	3838	2880	3648	1998	3192	2160	2655
6	2592	3025.8	2442	3159	2937	2450	2240	2112
7	2464	2312	2937	1425	2770.2	2400	3264	1938
8	3720	2635	2470	2805	3168	2760	3675.4	2464
9	1935.2	2341.5	1548	2021	1472	1917.8	1763	1711.2
10	2275	2610	1491	2815.2	2075	2242	1886	2204
11	2090	2610	1819.3	2562	1932	2016	901	2772
12	2176	1497.5	2720	1696	2240	1582.4	1698.3	1560
13	1716	3210	1645	2448	960	2863.8	2648.7	2490
14	3040	1628	3042	1386	2886	1518	2516	1536
15	1970	2340	1920	2242	1595	2200.8	2500	2062.8
MEAN	**2383**	**2637.3**	**2311.2**	**2572.5**	**2159.9**	**2387.1**	**2206**	**2310**
STD DEV	**610.5**	**872.4**	**520.9**	**938.8**	**572**	**664.2**	**654.6**	**713.2**

Graph 4.5.4: **Mean values for absolute count.**

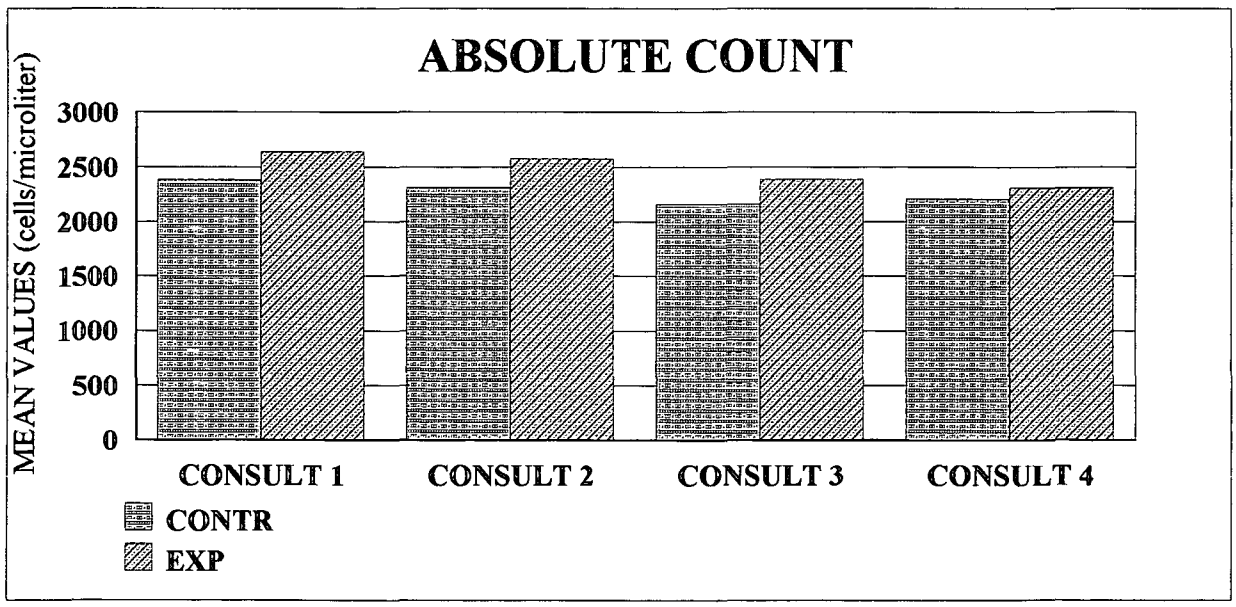

TABLE 4.5.4(b): Wilcoxon's Signed Rank Test for the Absolute count.

	CONTROL		EXPERIMENTAL	
	P-values	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	0.605574	0.516398	1	0
Consult 1 vs Consult 3	0.121335	1.54919	0.301698	1.0328
Consult 1 vs Consult 4	0.121335	1.54919	0.121335	1.54919
Consult 2 vs Consult 3	0.301698	1.0328	0.0388669	2.06559
Consult 2 vs Consult 4	0.305574	0.516398	0.605574	0.516398
Consult 3 vs Consult 4	1	0	0.121335	1.54919

In neither the control nor the experimental group was there a single statistically significant change at any time in terms of absolute count. The null hypothesis was therefore accepted.

TABLE 4.5.4(c): Mann-Whitney U-test for the Absolute count.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.455249	0.740018	0.406785	0.8357
Z- value	0.746688	0.331825	0.829561	0.20739

The null hypothesis was accepted for all four the Consultations which indicated that at the 5% level of significance no statistically significant difference occurred between the two groups at any time during the treatment period.

4.5.5: CD 3 COUNT

Table 4.5.5(a): **CD 3 count (no/cubic mm) in the experimental and control groups at each consultation.**

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	2147	1151	1863	1697	1535	1406	1281	977
2	1979	1520	1919	1700	1587	1805	1528	1687
3	637	3817	1359	3673	1435	3213	1244	3230
4	1774	2241	1879	2027	1753	1613	1805	2309
5	2102	2886	2140	2594	1530	2289	1648	1943
6	1853	2091	1702	2186	2082	1708	1637	1493
7	1860	1688	2256	975	2036	1726	2533	1421
8	1882	1706	1272	1666	1746	1650	2132	1562
9	1525	1833	1201	1584	1163	1509	1400	1304
10	1479	1955	965	2021	1367	1374	1218	1208
11	1264	1924	1095	1960	1264	1327	551	1938
12	1702	1030	2130	1092	1718	1067	1141	966
13	1126	2276	1117	1819	662	2197	2008	1875
14	2210	1304	2181	1059	2072	1193	1796	1184
15	1375	1484	1217	1217	1030	1303	1475	1262
MEAN	**1661**	**1927.1**	**1619.7**	**1818**	**1532**	**1692**	**1559.8**	**1623.9**
STD DEV	**416.2**	**683.7**	**444**	**661.6**	**385.9**	**522**	**456.5**	**567.4**

Graph 4.5.5: **Mean values for CD 3 count.**

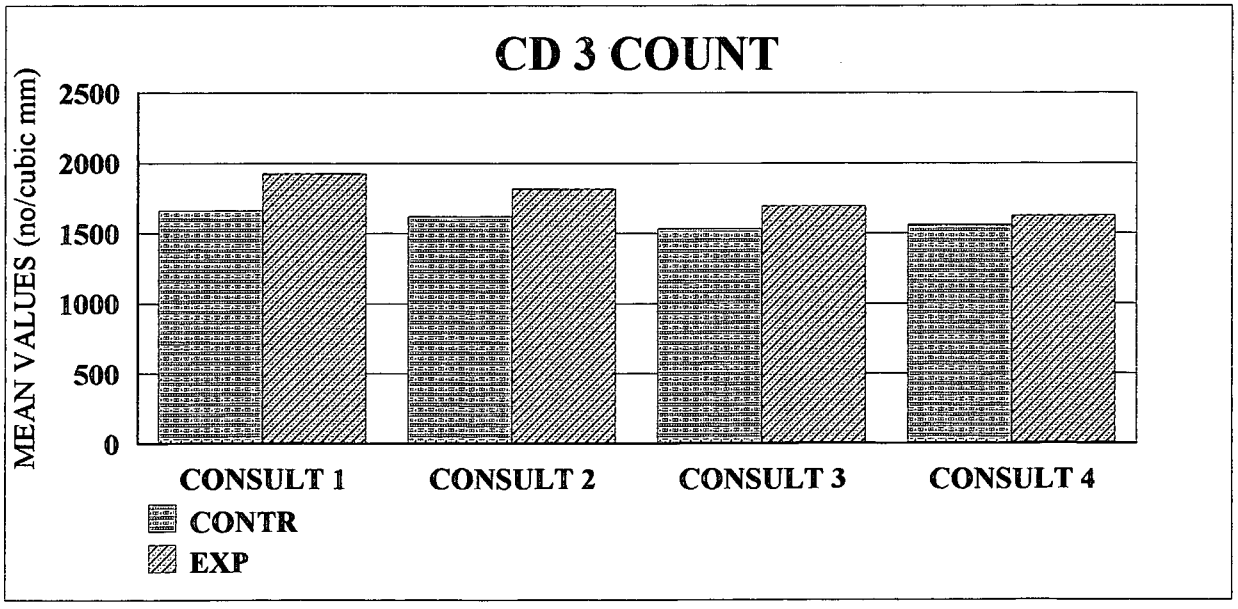

TABLE 4.5.5(b): Wilcoxon's Signed Rank Test for the CD 3 count.

	CONTROL		EXPERIMENTAL	
	P-values	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	0.301698	1.0328	0.605574	0.516398
Consult 1 vs Consult 3	0.181449	1.33631	0.121335	0.54919
Consult 1 vs Consult 4	0.605574	0.516398	0.0388669	2.06559
Consult 2 vs Consult 3	0.301698	1.0328	0.301698	1.0328
Consult 2 vs Consult 4	0.605574	0.516398	0.301698	1.0328
Consult 3 vs Consult 4	1	0	0.0388669	2.06559

In neither the control nor the experimental group was there a single statistically significant change at any time in terms of the CD 3 count. The null hypothesis was therefore accepted.

TABLE 4.5.5(c): Mann-Whitney U-test for the CD 3 count.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.4553	0.755705	0.678299	0.966909
Z- value	0.746605	0.31112	0.414781	-0.0414781

The null hypothesis was accepted for all four the Consultations which indicated that at the 5% level of significance no statistically significant difference occurred between the two groups at any time.

4.5.6: CD 4 COUNT

Table 4.5.6(a): CD 4 count (no/cubic mm) in the experimental and control groups at each consultation.

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	1471	671	1248	975	1057	796	897	580
2	1562	966	1489	1041	1194	1229	1183	449
3	523	1450	771	1969	542	1556	759	1447
4	1204	1541	1336	1328	1195	997	1229	1486
5	1120	1873	1054	1499	933	1462	806	1213
6	1120	1123	935	1393	1204	965	1120	923
7	1264	807	1201	544	1169	862	1541	692
8	1466	1145	795	1108	1109	1094	1422	786
9	826	1262	670	1116	631	1041	733	912
10	1190	1214	728	1154	1102	955	952	694
11	736	1138	542	1184	719	825	335	1092
12	1084	715	1384	782	1122	798	873	680
13	736	786	747	639	449	707	1383	627
14	1395	759	1481	584	1299	726	1215	656
15	660	894	634	843	573	775	963	802
MEAN	**1090.5**	**1089.6**	**1001**	**1077.3**	**953.2**	**985.9**	**1027.4**	**869.3**
STD DEV	**314.6**	**331.6**	**318.9**	**367.8**	**277.9**	**249**	**304.7**	**301.2**

Graph 4.5.6: Mean values for CD 4 count.

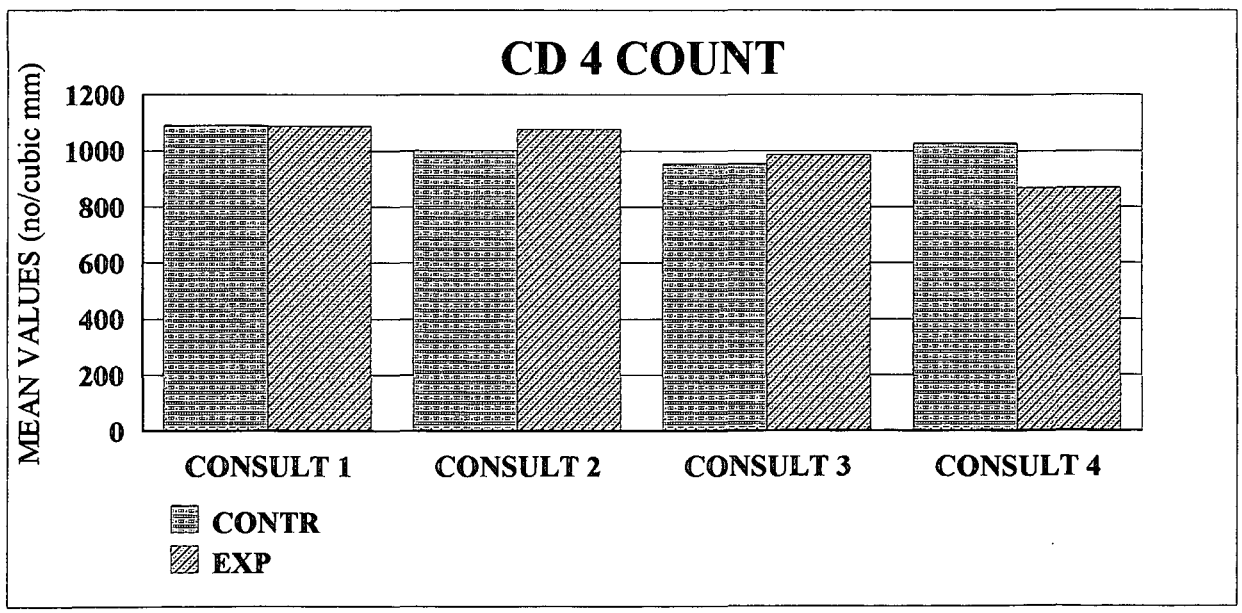

TABLE 4.5.6(b): Wilcoxon's Signed Rank Test for the CD 4 count.

	CONTROL		EXPERIMENTAL	
	P-values	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	0.301698	1.0328	0.605574	0.516398
Consult 1 vs Consult 3	0.0388669	2.06559	0.301698	1.0328
Consult 1 vs Consult 4	0.422676	0.801704	0.00030067	3.61478
Consult 2 vs Consult 3	0.121335	1.54919	0.301698	1.0328
Consult 2 vs Consult 4	1	0	0.0388669	2.06559
Consult 3 vs Consult 4	1	0	0.0388669	2.06559

A statistically significant change occurred between Consultation 1 versus Consultation 4 in the experimental group in terms of CD 4 count.

TABLE 4.5.6(c): Mann-Whitney U-test for the CD 4 count.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.966902	0.678299	0.900966	0.0890176
Z- value	-0.0414873	0.414781	-0.124434	-1.7006

The null hypothesis was accepted for all Consultation which indicated that at a 5% level of significance no statistically significant difference occurred between the two groups at any time during the treatment period.

4.5.7: CD 8 COUNT

Table 4.5.7(a): CD 8 count (no/cubic mm) in the experimental and control groups at each consultation.

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	615	505	702	843	663	620	370	431
2	719	595	707	715	397	678	502	283
3	279	2406	641	1683	430	1611	520	1770
4	615	719	630	778	634	518	678	810
5	1075	1174	1060	1218	727	1104	961	786
6	749	983	593	761	781	733	636	634
7	934	1020	1063	620	961	1037	1120	872
8	1495	604	951	682	1270	653	764	421
9	776	691	604	499	515	541	716	474
10	503	1039	346	1109	432	899	456	752
11	819	914	762	922	705	677	296	1001
12	596	472	802	494	661	502	447	431
13	446	1692	472	1256	286	1578	763	1320
14	891	505	840	428	863	417	717	521
15	651	753	682	688	533	671	673	631
MEAN	**744.2**	**938.1**	**723.7**	**846.4**	**657.2**	**816**	**641.3**	**742.5**
STD DEV	**278.7**	**500.9**	**192.6**	**330**	**241.8**	**356.4**	**212**	**377.1**

Graph 4.5.7: Mean values for CD 8 count.

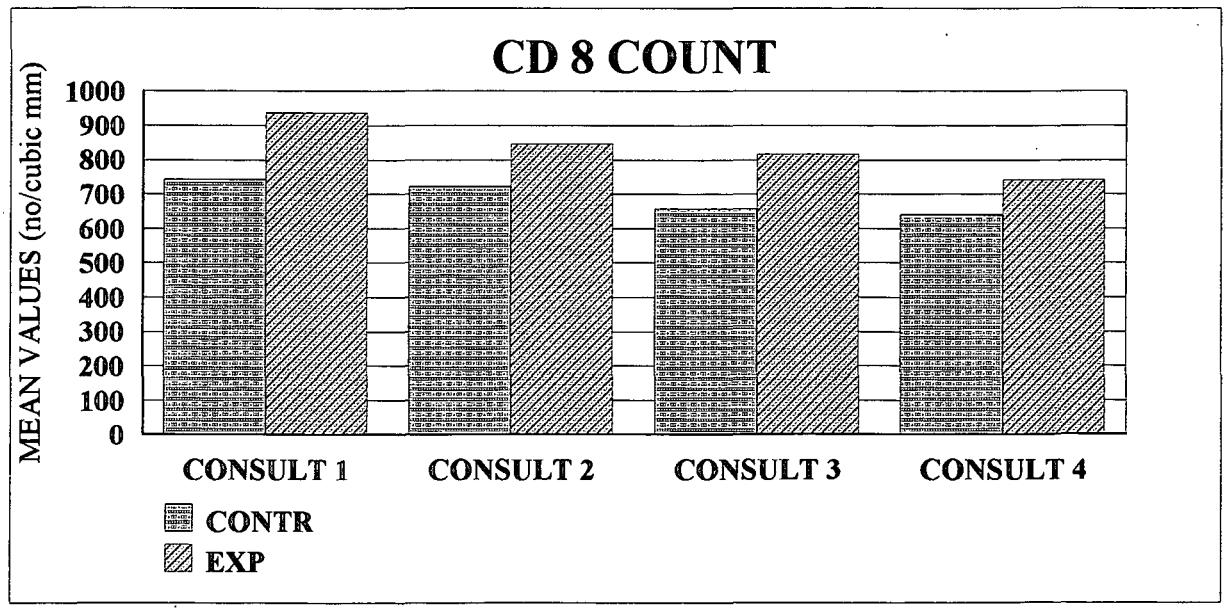

TABLE 4.5.7(b): Wilcoxon's Signed Rank Test for the CD 8 count.

	CONTROL		EXPERIMENTAL	
	P-values	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	1	0	1	0
Consult 1 vs Consult 3	0.605574	0.516398	0.301698	1.0328
Consult 1 vs Consult 4	0.301698	1.0328	0.0388669	2.06559
Consult 2 vs Consult 3	0.301698	1.0328	0.3121335	1.54919
Consult 2 vs Consult 4	0.605574	0.516398	0.605574	0.516398
Consult 3 vs Consult 4	0.605574	0.516398	0.121335	1.54919

In neither the control nor the experimental group was there a single statistically significant change at any time in terms of the CD 8 count. The null hypothesis was therefore accepted.

TABLE 4.5.7(c): Mann-Whitney U-test for the CD 8 count.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.394998	0.372457	0.280841	0.70889
Z- value	0.850584	0.891878	1.07843	0.373344

The null hypothesis was accepted for all four the Consultations which indicated that at the 5% level of significance no statistically significant difference occurred between the two groups at any time during the treatment period.

4.5.8: CD 2 COUNT

Table 4.5.8(a): CD 2 count (no/cubic mm) in the experimental and control groups at each consultation.

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	2268	1312	1784	1808	1573	1578	1386	1113
2	1973	1725	2447	1993	1880	1923	1848	1998
3	853	4018	1612	3868	1699	3341	1444	3372
4	1892	2460	1976	2089	1842	0	1923	2488
5	0	2909	1835	2725	1728	2327	1914	2028
6	2087	2227	295	2059	2470	2085	1805	1582
7	2001	1907	2323	1159	2152	1742	2667	1589
8	2987	1893	1914	2011	2515	1884	2867	1777
9	1662	1929	1311	1673	1236	1557	1490	1396
10	1663	2104	1090	2331	1500	1823	1394	1386
11	1563	2192	1368	2191	1493	1619	648	2414
12	1841	1133	2298	1262	1906	1223	1245	1084
13	1239	2661	1212	2059	725	2423	2220	2067
14	2505	1400	2519	1137	2387	1263	2035	1289
15	1249	1610	1325	1412	1110	1426	1528	1370
MEAN	**1718.9**	**2098.7**	**1687.3**	**1985.1**	**1747.7**	**1747.6**	**1760.9**	**1796.9**
STD DEV	**685**	**699.4**	**583.9**	**666.3**	**490.4**	**695.2**	**541.5**	**596.8**

Graph 4.5.8: Mean values for CD 2 count

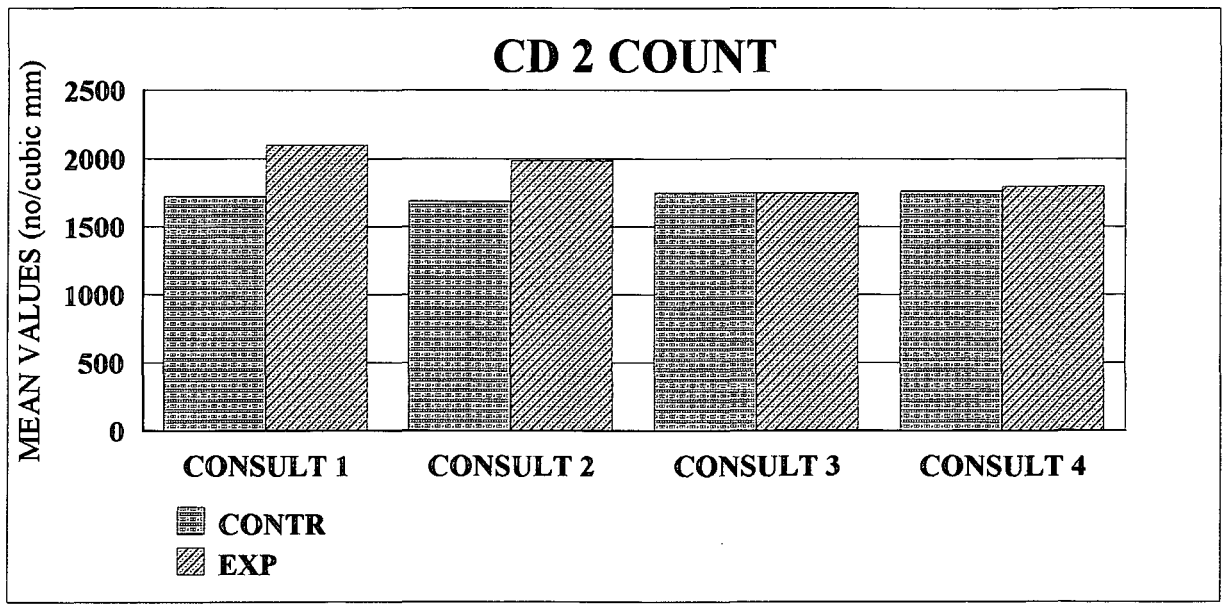

TABLE 4.5.8(b): Wilcoxon's Signed Rank Test for the CD 2 count.

	CONTROL		EXPERIMENTAL	
	P-values	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	1	0	0.301698	1.0328
Consult 1 vs Consult 3	0.301698	1.0328	0.038869	2.06559
Consult 1 vs Consult 4	0.605574	0.516398	0.038869	2.06559
Consult 2 vs Consult 3	0.301698	1.0328	0.301698	1.0328
Consult 2 vs Consult 4	1	0	0.605574	0.516398
Consult 3 vs Consult 4	1	0	0.301698	1.0328

In neither the control nor the experimental group was there a single statistically significant change at any time in terms of the CD 2 count. The null hypothesis was therefore accepted.

TABLE 4.5.8(c): Mann-Whitney U-test for the CD 2 count.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.245484	0.319451	1	0.884556
Z- value	1.16139	0.995584	0	-0.145189

The null hypothesis was accepted for all four the Consultations which indicated that at the 5% level of significance no statistically significant difference occurred between the two groups at any time during the treatment period.

4.5.9: CD 19 COUNT

Table 4.5.9(a): CD 19 count (no/cubic mm) in the experimental and control groups at each consultation.

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	408	181	335	306	328	202	85	195
2	173	257	148	291	147	398	113	302
3	200	858	306	1418	298	876	224	742
4	353	521	459	460	365	297	398	578
5	312	699	251	562	328	571	188	534
6	490	735	391	799	476	541	396	507
7	338	307	414	188	393	262	441	33
8	662	707	479	844	545	812	684	648
9	176	375	146	307	191	180	215	233
10	466	266	297	267	427	229	328	126
11	355	300	271	318	311	71	129	236
12	283	185	359	161	264	222	289	197
13	240	260	304	191	164	263	360	189
14	496	204	462	126	416	141	460	138
15	325	318	369	256	303	297	125	233
MEAN	**351.8**	**411.5**	**332.7**	**432.9**	**330.4**	**357.5**	**295.7**	**326.1**
STD DEV	**131.1**	**221.3**	**99.5**	**336.8**	**108.4**	**231.1**	**159.7**	**209.1**

Graph 4.5.9: Mean values for CD 19 count.

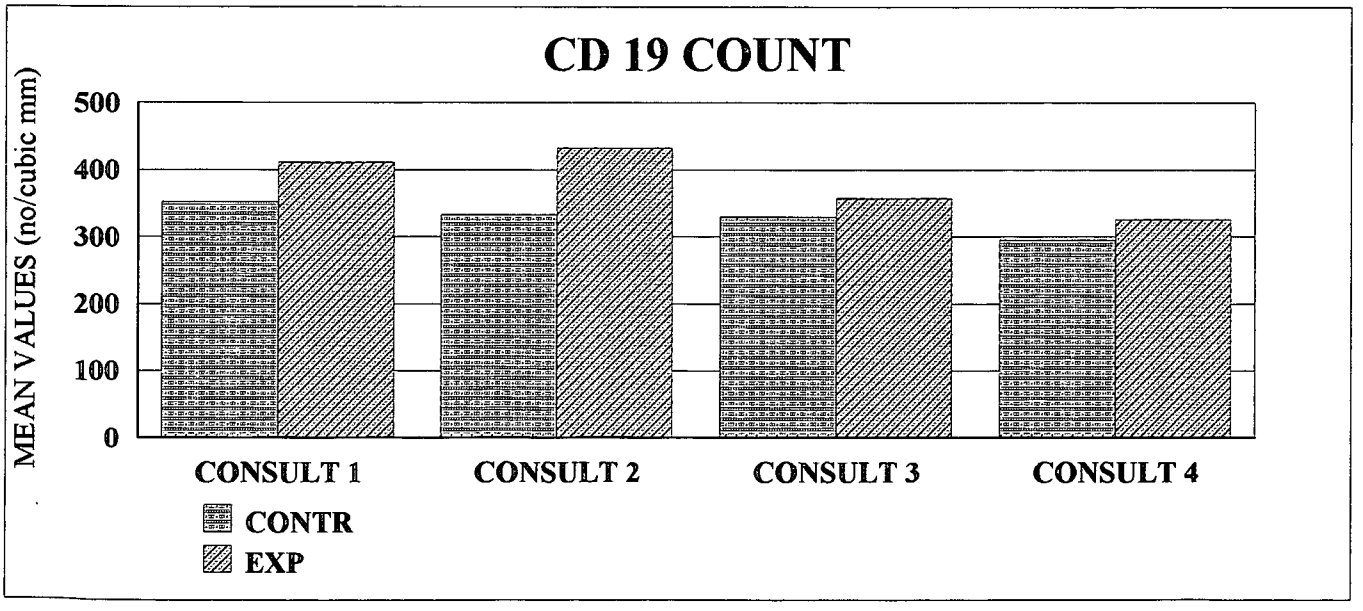

TABLE 4.5.9(b): Wilcoxon's Signed Rank Test for the CD 19 count.

	CONTROL		EXPERIMENTAL	
	P-values	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	0.605574	0.516398	1	0
Consult 1 vs Consult 3	0.301698	1.0328	0.605574	0.516398
Consult 1 vs Consult 4	1	0	0.121335	1.54919
Consult 2 vs Consult 3	0.605574	0.516398	1	0
Consult 2 vs Consult 4	0.605574	0.516398	0.121335	1.54919
Consult 3 vs Consult 4	1	0	0.0388669	2.06559

In neither the control nor the experimental group was there a single statistically significant change at any time in terms of the CD 19 count. The null hypothesis was therefore accepted.

TABLE 4.5.9(c): Mann-Whitney U-test for the CD 19 count.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.803458	0.917397	0.480631	0.708889
Z- value	248868	-0.103707	-0.705284	0.373344

The null hypothesis was accepted for all four the Consultations which indicated that at the 5% level of significance no statistically significant difference occurred between the two groups at any time during the treatment period.

4.5.10: CD 56 COUNT

Table 4.5.10(a): CD 56 count (no/cubic mm) in the experimental and control groups at each consultation.

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	168	255	167	287	165	163	113	143
2	696	255	662	413	442	220	396	480
3	127	593	339	302	398	136	291	151
4	172	314	174	283	156	248	220	216
5	309	576	161	398	228	284	402	242
6	295	103	73	130	103	54	202	70
7	207	222	217	205	211	86	193	271
8	874	99	450	213	551	216	500	195
9	132	117	54	123	56	136	157	101
10	193	238	151	439	129	274	198	66
11	196	311	291	315	201	296	89	421
12	207	201	223	98	155	128	105	122
13	127	273	130	171	60	226	244	129
14	131	116	183	143	176	82	101	134
15	206	402	223	489	166	396	123	334
MEAN	**269.3**	**271.7**	**233.2**	**267.3**	**213.1**	**196.3**	**222.3**	**205**
STD DEV	**211.5**	**148.7**	**149.8**	**121.4**	**136.9**	**91.9**	**120.8**	**120.5**

Graph 4.5.10: Mean values for CD 56 count.

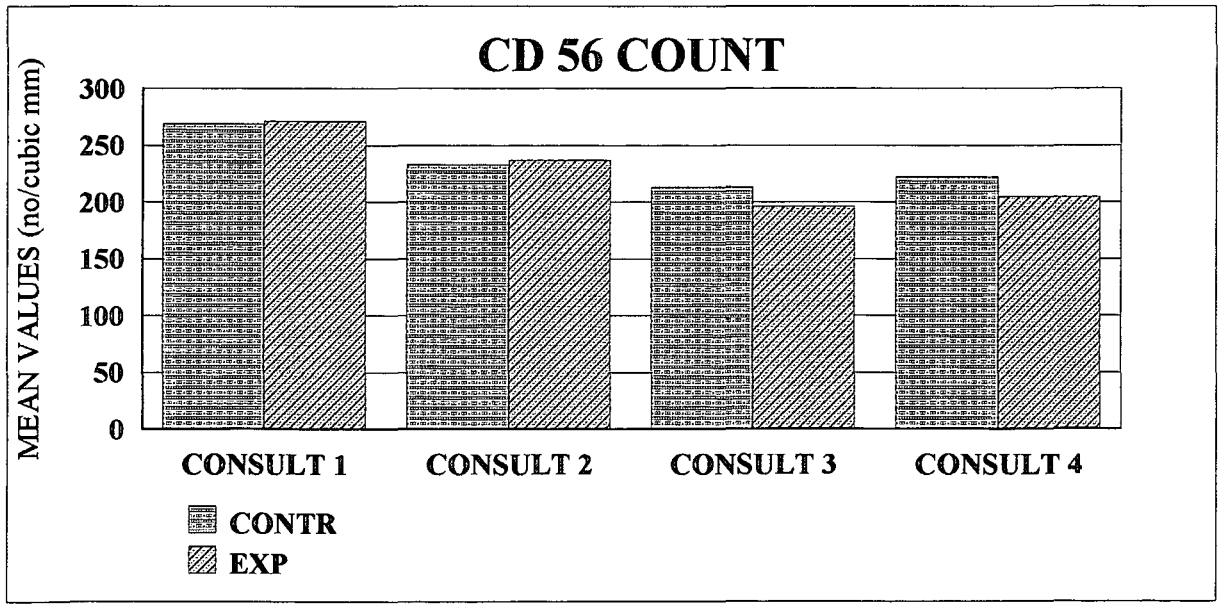

TABLE 4.5.10(b):Wilcoxon's Signed Rank Test for the CD 56 count.

	CONTROL		EXPERIMENTAL	
	P-values	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	1	0	0.605574	0.516398
Consult 1 vs Consult 3	0.121335	1.54919	0.0388669	2.06559
Consult 1 vs Consult 4	0.605574	0.516398	0.301698	1.0328
Consult 2 vs Consult 3	0.301698	1.0328	0.121335	1.54919
Consult 2 vs Consult 4	1	0	0.121335	1.54919
Consult 3 vs Consult 4	0.605574	0.516398	0.605574	0.516398

In neither the control nor the experimental group was there a single statistically significant change at any time in terms of the CD 56 count. The null hypothesis was therefore accepted.

TABLE 4.5.10(c): Mann-Whitney U-test for the CD 56 count.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.53369	0.467819	0.966905	0.693514
Z- value	0.622379	0.726028	0.0414827	-0.394085

The null hypothesis was accepted for all four the Consultations which indicated that at the 5% level of significance no statistically significant difference occurred between the two groups at any time during the treatment period.

4.5.11: CD 45 RA COUNT

Table 4.5.11(a): CD 45 RA count (no/cubic mm) in the experimental and control groups at each consultation.

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	2097	929	1583	1413	1442	1215	1338	791
2	1555	1270	1797	1442	1354	1516	1314	1483
3	654	3675	1244	3694	1407	2797	1133	2777
4	1558	2013	1724	1898	1435	1485	1516	2103
5	1833	2740	1886	2670	1369	2257	1644	1736
6	1853	2415	1538	2287	1941	1742	1593	1654
7	1363	1334	1389	818	1596	1186	1782	1145
8	0	1844	1487	1980	1806	1992	2021	1727
9	939	1506	755	1326	689	1231	931	1090
10	1083	1428	716	476	975	1291	868	1093
11	1580	1999	1388	1978	1445	1486	653	2195
12	1197	1050	1409	1163	1089	1122	1073	1020
13	1074	2562	1068	1875	618	2262	1393	1920
14	2247	1177	2108	1008	2092	1081	1897	1126
15	1292	1587	1340	1469	1078	1461	1660	1399
MEAN	**1451.8**	**1835.3**	**1428.8**	**1699.8**	**1355.7**	**1608.3**	**1387.7**	**1550.6**
STD DEV	**436.7**	**725.9**	**371.5**	**769.1**	**404.3**	**488.3**	**383.4**	**522.1**

Graph 4.5.11: Mean values for CD 45 RA count.

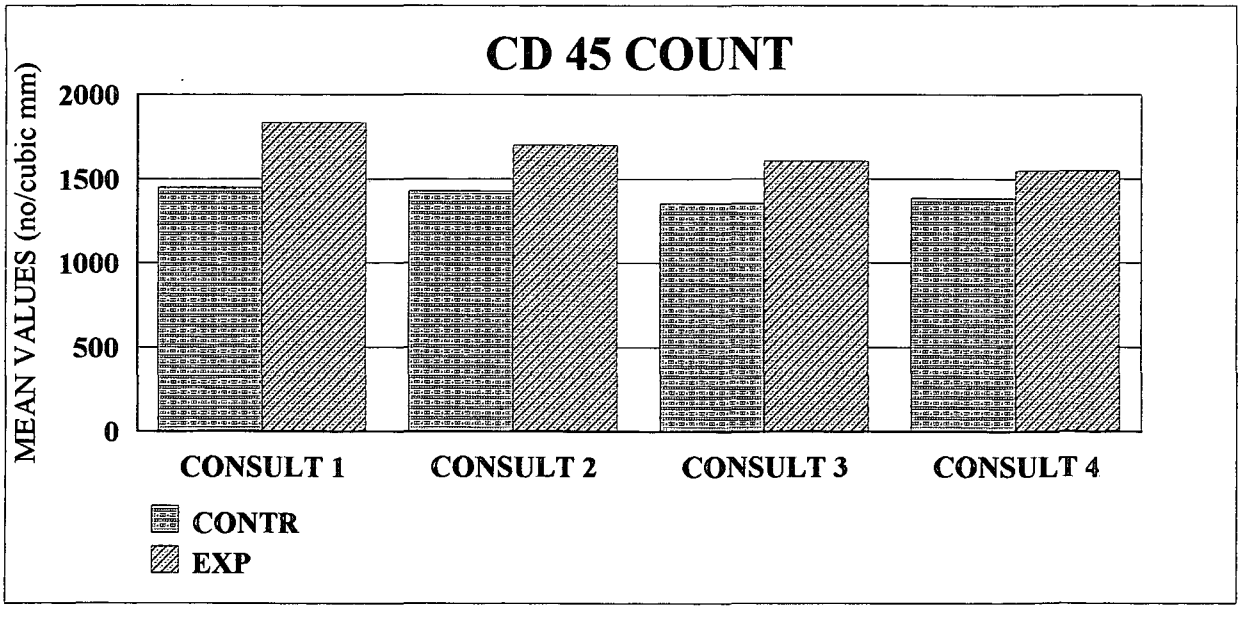

TABLE 4.5.11(b): Wilcoxon's Signed Rank Test for the CD 45 RA count.

	CONTROL		EXPERIMENTAL	
	P-values	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	0.789264	-0.267261	0.301698	1.0328
Consult 1 vs Consult 3	0.0613685	1.87083	0.121335	1.54919
Consult 1 vs Consult 4	0.181449	1.33631	0.0388669	2.06559
Consult 2 vs Consult 3	0.605574	0.516398	0.605574	0.516398
Consult 2 vs Consult 4	1	0	1	0
Consult 3 vs Consult 4	1	0	0.0388669	2.06559

In neither the control nor the experimental group was there a single statistically significant change at any time in terms of CD 45 RA count. The null hypothesis was therefore accepted.

TABLE 4.5.11(c): Mann-Whitney U-test for the CD 45 RA count.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.230061	0.361495	0.198505	0.4553
Z- value	1.2002	0.912517	1.28582	0.746605

The null hypothesis was accepted for all four the Consultations which indicated that at the 5% level of significance no statistically significant difference occurred between the two groups at any time during the treatment period.

4.5.12: CD 29 COUNT

Table 4.5.12(a): **CD 29 count (no/cubic mm) in the experimental and control groups at each consultation.**

	CONSULT 1		CONSULT 2		CONSULT 3		CONSULT 4	
PATIENT	CONTR	EXP	CONTR	EXP	CONTR	EXP	CONTR	EXP
1	1531	1059	1385	586	1172	940	813	937
2	1255	898	1908	1768	420	1766	1660	1616
3	379	4175	706	3868	1486	2699	1362	2345
4	1177	1842	785	1598	1324	981	1766	1763
5	0	2779	323	2422	663	2011	1339	1309
6	1384	1086	310	287	576	1803	1279	860
7	1772	1406	2159	844	2211	271	2657	1349
8	2329	580	2149	1287	2458	1536	3194	1441
9	1566	1239	1266	1619	1198	1277	1299	1496
10	1893	1524	1157	2331	1554	1603	1277	1644
11	1202	1441	1250	1722	1177	1395	567	2464
12	1723	894	2081	945	1711	1052	1274	903
13	1217	2748	1201	1518	733	2056	2055	1544
14	1803	1057	1923	794	1882	965	1570	1048
15	1486	1523	1576	1599	1337	1532	1773	1285
MEAN	**1381.1**	**1616.7**	**1345.3**	**1545.9**	**1326.8**	**1459.1**	**1592.3**	**1466.9**
STD DEV	**560**	**912.2**	**603.6**	**850.9**	**567.8**	**565.6**	**639.9**	**456.7**

Graph 4.5.12: **Mean values for CD 29 count.**

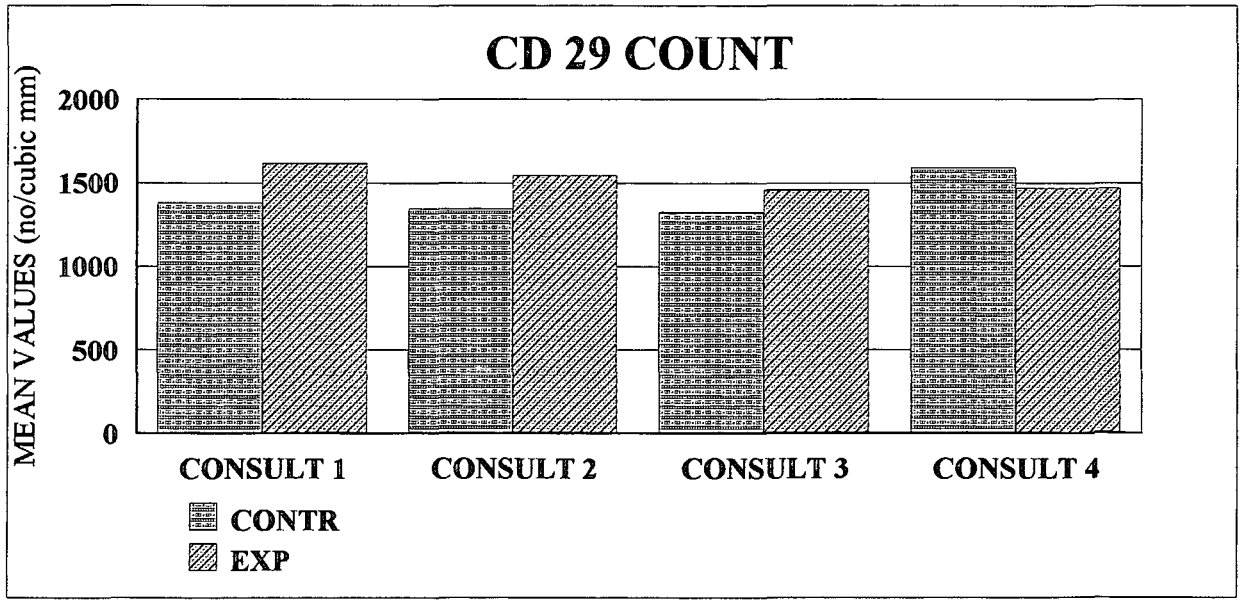

TABLE 4.5.12(b): Wilcoxon's Signed Rank Test for the CD 29 count.

	CONTROL		EXPERIMENTAL	
	P-values	**Z-values**	**P-values**	**Z-values**
Consult 1 vs Consult 2	1	0	1	0
Consult 1 vs Consult 3	0.605574	0.516398	1	0
Consult 1 vs Consult 4	1	0	0.605574	0.516398
Consult 2 vs Consult 3	1	0	0.605574	0.516398
Consult 2 vs Consult 4	0.301698	1.0328	1	0
Consult 3 vs Consult 4	0.605574	0.516398	0.605574	0.516398

In neither the control nor the experimental group was there a single statistically significant change at any time in terms of CD 29 count. The null hypothesis was therefore accepted.

TABLE 4.5.12(c): Mann-Whitney U-test for the CD 29 count.

	Consult 1	**Consult 2**	**Consult 3**	**Consult 4**
P - value	0.771547	0.589736	0.533827	0.740018
Z- value	-0.290346	0.539215	0.622171	-0.331825

The null hypothesis was accepted for all four the Consultations which indicated that at the 5% level of significance no statistically significant difference occurred between the two groups at any time during the treatment period.

4.6 DEMOGRAPHIC DATA

TABLE 4.6.1 Demographic data

	CONTROL	EXPERIMENTAL	TOTAL
AGE DISTRIBUTION			
Age Range	19 - 49	23 - 49	19 - 49
Average Age	37.27	36.07	36.67
GENDER DISTRIBUTION			
Males	4	11	15
Females	11	4	15
RACIAL DISTRIBUTION			
Black	2	-	2
White	4	6	10
Indian	9	9	18

CHAPTER 5

5. DISCUSSION

5.1 INTRODUCTION

The results are discussed in three parts: objective data, subjective data and blood and lymphocyte profiles.

Although the purpose of this study was to see whether a significant change occurred over the entire study period, data from the second and third consultations were included in the discussion.

5.2 OBJECTIVE DATA

5.2.1 Lumbar Spine Ranges of Motion

5.2.1.1 Intra-group comparison

When the overall treatments were evaluated, there were statistically significant changes in the experimental group in terms of left rotation ($p = 0,0161569$) and right rotation ($p = 0,0019$) over the entire treatment

period. Statistically significant changes also occurred in the experimental group in terms of right rotation between consultation 1 and consultation 3 ($p = 0{,}005546$). No statistically significant changes were found in any of the lumbar spinal ranges of motion in the placebo group. These findings suggested that, over the entire study period, the experimental group responded somewhat better than the placebo group in terms of increasing rotational ranges of motion.

5.2.1.2 Inter-group comparison

A statistical comparison between the two groups failed to show any statistically significant differences in any of the parameters measured. These results suggest a similarity between the two groups in terms of improvement of ranges of motion.

5.2.2 Algometric Readings

5.2.2.1 Intra-group comparison

No statistically significant improvement was found in either the experimental or placebo group over the entire study period.

5.2.2.2 Inter-group comparison

When the results of the two groups were compared using the Mann-Whitney U-test it was found that a statistical significant difference existed between the two groups in terms of Algometer readings at the third consultation (p = 0,00299763). No statistical significant difference was noted between the two groups during the other consultations.

5.2.3 Interpretation of Objective findings

When analysing the statistics from the objective data in this study, the experimental group showed statistical significant improvement in, left and right rotation over the entire treatment period. This indicated that two of the six lumbar spine ranges of motion had statistical significant changes over the treatment period in the experimental group. The control group however, failed to show any statistically significant changes over the treatment period.

When the inter-group results were analysed it was somewhat disappointing to note that the experimental group did not show any statistical significant improvement when compared to the control group. An important observation that the experimental group clinically performed better than the control group over the entire treatment period was noted in all six lumbar spine ranges of motion.

The results of this study does not agree with studies done by Doran and Newel (1975), Evens et al. (1978), and Pope et al. (1994) who all reported statistically significant differences in terms of objective findings in patients receiving spinal manipulative therapy. The present study however support findings by Waagen et al. (1986) who compared the effect of chiropractic and sham adjustments on patients. They found no statistically significant differences for flexion, extension, left and right lateral flexion, even though subjects were treated two to three times a week for two weeks. The only statistically significant difference Waagen et al. (1986) found, were for active straight leg raise on the right.

If the subjects in the present study were treated more frequently and over a longer period of time, the results might have been a greater statistically significant difference. The present study also supports findings by Meade et al. (1990) where no statistically significant differences were found in flexion, extension, left and right lateral flexion.

In terms of Algometric readings the experimental group responded better, but only at the third consultation. No statistically significant changes occurred in either of the two groups over the treatment period. The results of the present study support finding by Terret and Vernon (1984) where statistically significant differences were found in patients receiving chiropractic versus placebo treatment in terms of sensitivity to pain.

5.3 SUBJECTIVE DATA

5.3.1 Numerical Rating Scale 101 (NRS 101)

5.3.1.1 Intra-group comparison

When the results in terms of pain perception were evaluated, statistically significant changes (p = 0,00149629) were found in the control group, between the first and last consultation. No statistically significant changes were found in the experimental group.

5.3.1.2 Inter-group comparison

A comparison between the two groups failed to show any statistically significant difference and suggest a similarity between the two groups in terms of pain perception.

5.3.2. Short-form McGill Pain Questionnaire

5.3.2.1. Intra-group comparison

When analysing the results in terms of the Short-form McGill Pain Questionnaire, both the control (p = 0,0051209) and the experimental (p

= 0,0019459) groups showed statistically significant changes over the entire treatment period. Statistically significant changes also occurred in the control group between consultation 1 and 3 (p = 0,0161564).

5.3.2.2. Inter-group comparison

A statistically comparison between the two groups failed to show any statistically significant difference.

5.3.3. Oswestry Back Disability Index

5.3.3.1. Intra-group comparison

When the results were evaluated, there were statistically significant changes (p = 0,0098) in the experimental group over the entire treatment period. Statistical significant changes were also found between consultations 2 and 4 (p = 0,00554577) and consultations 3 and 4 (p = 0,0096748). No statistically significant changes were found in the control group.

5.3.3.2. Inter-group comparison

No statistically significant changes were found between the two groups

over the entire study.

5.3.4. Interpretation of Subjective findings

The subjective data indicated that spinal manipulative therapy was less effective than placebo in decreasing sensitivity to pain. However, when using the Oswestry Back Disability Index, only the spinal manipulative therapy group showed a statistically significant improvement over the treatment period. When using the Short-form McGill Pain Questionnaire, both the control and experimental group showed statistically significant changes over the entire treatment period.

The results of the subjective data indicated that the spinal manipulative therapy group was not more effective than the control group in terms of pain intensity and disability. The results of this study did not agree with the results of the studies done by Evans et al. (1978), Meade et al. (1990) and Triano et al. (1995) where it was found that the groups receiving spinal manipulation had significant reductions in pain and disability. Only the experimental group in the present study seemed to be effective in improving disability. The reasons for this is not clear. The studies done by Doran and Newell (1975) and Pope et al. (1995) demonstrated that there were no statistically significant difference between treatment groups in terms of subjective findings. The present study support these findings.

The reason for the improvement in the control group in terms of the Numerical Rating Scale 101, whilst the experimental group did not, is difficult to explain. Even in other studies with similar samplings, significant changes have been noted. It could have been due to chance that with these sample sizes, sooner or later, this might have happened. The possibility also exists that the gender distribution in the two groups may have somehow influenced this outcome, although the author is unaware of any evidence to support this. It could also be attributed to the subject's psychological perception to pain. Patients indicated that it was difficult to put a value to their pain. Numerous individual and culture factors, including sex, upbringing, personality and age have been shown to influence a person's response to pain. (McDowell 1996:335). The gender distribution in the present study was not equal in both groups, which could have had an effect on the interpretation of pain.

5.4 BLOOD AND LYMPHOCYTE PROFILES

5.4.1 Intra-group comparison

With the exception of CD 4 ($p = 0{,}0003$) in the experimental group, no statistically significant changes were noted in any of the two groups, in terms of blood and lymphocyte profiles over the study period.

5.4.2 Inter-group comparison

When results of the two groups were compared in using the Mann-Whitney U-Test in terms of haemoglobin levels, it was found that a statistical significant difference existed between the two groups at all times of data collection (p-value for consultation 1 = 0,00692814; consultation 2 = 0,0120356; consultation 3 = 0,0179513; consultation 4 = 0,00938822). No statistically significant changes were found in any of the other parameters measured.

5.4.3 Interpretation of blood and lymphoeyte profiles

The haemoglobin, white cell, platelet and absolute counts were done to determine if any of the subjects were immunologically compromised. The values reported in this study are within the reference ranges for normal human subjects between the ages of 1 8 and 75 years (Reichert, et al. 1991).

The haemoglobin values were the only parameter that showed a statistical significant difference between the two groups. This difference was observed at consultation 1 and remained throughout the treatment period. The difference could possibly be attributed to the higher number of females in the control group and the higher number of males in the experimental group. Although this difference was statistically significant, it was well within the reference ranges of

14 to 1 8 g/dL for men and 12 to 16 g/dL for females in both groups (Braunwald, et al. 1987: A2).

With regard to the immunophenotypes, this study failed to demonstrate a significant treatment effect over the study period. The results of the present study however, agree with the results of the study done by Brennan, et al. (1994), where no significant treatment effect took place in lymphocyte subsets in the manipulated group.

The reason why a statistical significant difference between consultation 1 and 4 ($p = 0{,}00030067$) with regard to the CD 4 count, is unclear. However, this may be an area pursue in future studies.

5.5 DEMOGRAPHIC DATA

The average ages and the age ranges denote a fairly even distribution of gender within this study. When lolling at the gender, a rather uneven distribution of patients was found which could have had an effect on haemoglobin levels, affecting inter-group analysis. The author of the present study is not sure whether the uneven gender and racial distribution could have had any physiological influences on the other parameters measured.

5.6 COMMENT

It was difficult to compare the results of this study to previous studies, as this was the first study to utilise clinical and haemotological data to determine the effect of spinal manipulative therapy in patients with mechanical low back pain. It was also difficult to interpret the statistics obtained from the subjective and objective data and blood tests as the results of some parameters improved in the experimental groups, whilst others improved in the control group. Perhaps if spinal manipulative therapy were continued until a clear clinical improvement established itself, the haematological data might have been different.

CHAPTER 6

CONCLUSIONS AND RECOMMENDATIONS

Thirty subjects completed this study to determine the efficacy of spinal manipulative therapy compared to placebo for chronic low back pain in terms of clinical and immune cellular responses.

One of the disappointing aspects of this study was that the only significant improvement of the experimental group over the control group was in terms of the Algometer readings at the third visit. However, an interesting trend was that there appeared to be an improvement in the pain intensity in the experimental group towards the end of the study, given that each group received only three adjustments over a two week period. Because the two groups were not stratified, two biases crept in, namely a preponderance of females in the control group and the same group having significantly higher haemoglobin levels. Otherwise the two groups were similar in all respects.

Statistically significant subjective changes occurred in the control group in terms of pain perception as measured by the Numerical Rating Scale 101 and the Short-form McGill Pain Questionnaire. Pain perception in the experimental group also showed a statistically significant improvement measured by the Short-form McGill Pain Questionnaire.

The experimental group also showed an increase in functional activities that were previously affected by back pain, indicated by the scores of the Oswestry Back Disability Index.

However the results of the Oswestry Back Disability Index; the Short-form McGill Pain Questionnaire and the Numerical Rating Scale 101 failed to show any statistically significant differences between the two groups. The spinal manipulative group did no better in any area than the control group.

Statistical significant differences in terms of haemoglobin levels were noted between the two groups, throughout the treatment period. This can probably be attributed to the difference in male to female ratio in the two groups. For the experimental group, the CD 4 count was the only immunophenotype where a statistical significant change took place over the treatment period, but there was no difference when compared to the control group.

The results of this study are based on a small number of patients and require confirmation and modification, using a larger sample size, so as to represent the normal distribution. Long term trials in which patients are treated and monitored for longer periods are also recommended.

REFERENCES

Ader, R., Cohen, N and Felten D. 1995. Psychoneuroimmunology: interactions between the nervous system and the immune system. Lancet. 345: Jan-March. pp 99-103.

Alcorn, S.M. 1977. Chiropractic treatment and antibody levels. Journal of Australian Chiropractors' Association Spine.11(3): 18-37.

Allen, J.M. 1993. The effects of chiropractic on the immune system: A review of the literature. Chiropractic Journal of Australia. 23(4): 132 - 135.

Anderson, J.E. 1985. Lumbar facet arthropothy and injection: a preliminary report. Clinical Journal of Washington Chiropractic Association. 3(1):24-27.

Anderson, R., Meeker, W.C., Wirick, B.E., Mootz, R.D., Kirk, D.H. and Adams, A.H. 1992. A meta-analysis of clinical trials of spinal manipulation. Journal of Manipulative and Physiological Therapeutics. 15(3): 181-194.

Bellanti, J.H. 1979. Immunology: basic processes. 2nd ed. Philadelphia: W.B. Saunders. p. 214. ISBN 0-7216-1244-X.

Besedovsky,H.O., del Ray, A and Sorkin, E. 1986. Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. Science 233:652-654.

Bernard, T.N. and Kirkaldy-Willis, W.H. 1987. Recognizing specific characteristics of nonspecific low back pain. Clinical Orthopaedics, 217: 266-280.

Beurger, A.A. 1983. Experimental neuromuscular models of spinal manual techniques. Manual Medicine. 1:10-17.

Bogduk, N. and Engel, R. 1983. The menisci of the lumbar aygapophyseal joints: a review of their anatomy and clinical significance. Spine. 9:454-460.

Bogduk, N. and Twomey, L.T. 1991. Clinical Anatomy of the Lumbar Spine. 2nd ed. London: Churchill Livingstone Inc. 197p. ISBN 0-443-04339-6.

Bourdillon, J.F., Day, E.A. and Bookhout, M.R. 1992. Spinal Manipulation. 5th ed. Oxford. Butterworth Heineman Ltd. 381p. ISBN 0-7506-0576-6.

Braunwald, E. , Isselbacher, K.J., Petersdorf, R.G., Wilson, D., Martin, J.B., Fauci, A.S. Principles of Internal Medicine. New York: MGraw Hill Book Company. 872p. ISBN 07-007261-2.

Brennan, P.C., Graham, M.A., Triano, J.J., Hondras, M.A. and Anderson, R.J. 1994. Lymphocyte profiles in patients with chronic low back pain enrolled in a clinical trial. Journal of Manipulative Physiological Therapeutics. 17: 219-227.

Brennan, P.C., Hondras, M.A. 1989. Priming of neutrophils for enhanced respiratory burst by manipulation of the thoracic spine. In: Proceedings of the International Conference on Spinal Manipulation. Arlington, Virginia: Foundation for Chiropractic Education and Research.

Brennan, P.C., Kokjohn, K., Kaltinger, C.J., Lohr, G.E., Glendening, C., Hondras, M.A., McGregor, M and Triano, J.J. 1991. Enhanced phagocytic cell respiratory burst induced by spinal manipulation: Potential role of Substance P. Journal of Manipulative and Physiological Therapeutics. 14(7): 399-407.

Brennan, P.C., Triano, J.J., McGregor, M., Kokjohn, K., Hondras, M.A. and Brennan, D.C.. 1992. Enhanced neutrophil respiratory burst as a biological marker for manipulation forces: Duration of the effect and association with Substance P and tumor necrosis factor. Journal of Manipulative and Physiological Therapeutics. 15(2): 83-89.

Bronfort, G. 1989. Chiropractic versus general medical treatment of low back pain: a small scale controlled clinical trial. American Journal of Chiropractic Medicine. 2:145-150.

Burton, C.V. and Cassidy, J.D. 1992. Economics, epidemiology and risk factors. In Kirkaldy-Willis, W.H. ed. Managing Low Back Pain. 3rd ed. New York: Churchill Livingstone Inc. 418p. ISBN 0-443-0853508.

Cailliet, R. 1988. Low Back Pain Syndrome. 4th ed. USA: F.A. Davis Company. 341p. ISBN: 0-8036-1606.

Cats-Baril, W.L. and Frymoyer, J.W. 1991. The economics of spinal disorders. In Frymore, J.W. (Ed). The Adult Spine: Principles and Practice. New York: Raven Press, Ltd. 2178p. ISBN: 0-88167-689-6 (set).

Cox, J.M. 1979. Low Back Pain: Recent statistics and data on its mechanism, diagnosis and treatment from chiropractic manipulation. The Americal Chiropractic Association Journal of Chiropractic. 13: 125-138.

Cox, J.M. 1985. Low back pain: Mechanisms, Diagnosis and Treatment. 4th ed. Baltimore: Williams and Wilkins. 384p. ISBN: 0-683-02151-6.

Coxhead, C.E., Inskip, H., Meade, T.W., North, W.R.S. and Troup, J.D.G. 1981. Multicentre trial of physiotherapy in the management of sciatic symptoms. Lancet. 1: 1065-1068.

Cyriax, J. 1977. Textbook of Orthopaedic Medicine. Volume 2: treatment by manipulation, massage and injection. 9th ed. London: Bailiere Tindall. 462p. ISBN 0-7020-06386.

Danek, A., O'Dorisio, M.S. and O'Dorisio, T.M. 1988. Specific binding sites for vasoactive intestinal polypeptide on nonadherent peripheral blood lymphocytes. Journal of Immunology. 131:1173-77.

De Boer, K.F., Schutz, M. and McKnight, M.E. 1988. Acute effects of spinal manipulation on gastrointestinal myoelectric activity in conscious rabbits. Manual Medicine. 3: 85-94.

Doran, D.M. and Newell, D.J. 1975. Manipulation in treatment of low back pain: A multicentre study. British Medical Journal, 2: 161-164.

Evans, D.H. 1994. The reliability of assessment parameters: accuracy and palpation technique. In Boyling, J.D. and Palastanga, N. Grieve's Modern Manual Therapy: The vertebral column. 2nd ed. New York: Churchill Livingstone. 870p. ISBN: 0-443-04348-5.

Evans, D.P., Burke, M.S., Lloyd, K.N., Roberts, E.E. and Roberts, G.M. 1978. Lumbar spine manipulation on trial. Part 1: Clinical Assessment. Rheumatological Rehabilitation. 17: 46-53.

Fairbank, J.C.T., Davies, J.B., Mboat, J.C., Einstein, S. and O'Brien, J.P. 1980. Oswestry Low Back Pain Disability Questionaire. Physiotherapy. 66.

Felten, D.L., Felten, S.Y. and Bellinger, D.L. 1987. Noradrenergic sympathetic neural interaction with the immune system; structure and function. Immunological Reviews. 100: 225-260.

Fidelibus, J.C. 1989. An overview of neuroimmunomodulation and a possible correlation with musculoskeletal system function. Journal of Manipulative Physiological Therapeutics. 12(4): 289-292.

Fischer, A.A. 1987. Pressure threshold measurements for diagnosis of myofascial pain and evaluation of treatment results. Clinical Journal of Pain. 2(4): 207-214.

Foreman, J.C. and Jordan, C.C. 1984. Neurogenic inflammation. Trends Pharmacological Science. 5:116-19.

Frymoyer, J.W. 1988. Back pain and sciatica. The New England Journal of Medicine. 318: 291-300.

Gatterman, M.I. 1990. Chiropractic Management of Spine Related Disorders. Baltimore: Williams and Wilkins. 437p. ISBN: 0-683-03438-3.

Gatterman, M.I. and Panzer, D. 1990. Disorders of the lumbar spine. In Gatterman, M.I. Chiropractic Management of Spine Related Disorders. Baltimore: Williams and Wilkins. 437p. ISBN: 0-683-03438-3.

Gatti, G., DelPonte, D., Cavallo, R. 1987. Circadian changes in human natural killer cell activity. Progressive Clinical Biological Research. A227:299-409.

Geiringer, S.R., Kincaid, C.B., Rechtien, J.J. 1988. Traction. Manipulation and massage. In de Lisa, J.A. ed. Rehabilitation Medicine: Principles and Practice. Philadelphia, Pa: JB Lippincott Company. 903p. ISBN 0-3975-0764-X.

Giles, L.G.F. 1989. Anatomical basis of low back pain. Baltimore: Williams and Wilkins. 197p. ISBN 0-683-03525-8.

Gitelman, R. 1975. Treatment of pain by spinal manipulation. In Goldstein, M (ed). Workshop on research status of spinal manipulative therapy. National Institute of Health, Education and Welfare publication 76-998, NINCDS. Monograph, No 15. Maryland: Bethesda. 352p.

Goetzl, E.J., Chernow, T., Renold, F. and Payan, D.G. 1985. Neuropeptide regulation of the expression of immediate hypersensitivity. Journal of Immunology. 135(suppl): 802-05.

Gulezian, R.C. 1979. Statistics for Decision Making. Philadelphia: W.B. Saunders. p 335. ISBN 0-7216-4350-7.

Guyton, A.C. and Hall, J.E. 1996. Textbook of medical physiology. 9th ed. Philadelphia: WB Sanders. pp. 612. ISBN 0-7216-5944-6.

Guyton, A.C. 1986. Textbook of medical physiology. 7th ed. Philadelphia: WB Sanders. pp. 553. ISBN 0-7216-1260-1.

Haldeman, S. 1992. Principles and Practice of Chiropractic. Norwalk, Connecticut/San Mateo, California: Appleton & Lange. pp 574. ISBN 0-8385- 6360-0.

Haldeman, S. 1993. Research supporting the efficacy of chiropractic manipulation. Presented at the South African International Chiropractic Conference, Sun City, Transvaal. 13 October 1993.

Halper, J. 1991. Immunocyte receptors and second messengers in psyconeuroimmunology. In Gorman, J.M. and Kertzner, R.M. Psychoimmunology Update. 1st ed. Washington D.C. American Psychiatric Press, Inc. 172p. ISBN 0-88048-450-0.

Heijnen, C.J., Kavelaars, A., and Ballieux, R.E. 1991. b-endorphine : cytokine and neuropeptide. Immunological Review. 119:41-63

Herberman, R.B., and Ortaldo, J.R. 1981. Natural killer cells, their role in defence against disease. Science. 214: 24-30.

Hirsch, D., Ingelmark, B. and Miller, M. 1963. The anatomical basis for low back pain. Acta Orthopedica Scandanavia. 33:1.

Hoehler, F.K. and Tobis, J.J. 1982. Low back pain and its treatment by spinal manipulation: measures of flexibility and assymmetry. Rheumatology Rehabilitation. 21:21-26.

Homewood, A.E. 1977. The Neurodynamics of the Vertrabral Sublaxation. 3rd ed. St. Petersburg, FL, Valkyrie Press. 385p. ISBN 0-683-0352-3.

Jackson, J.C., Cross, R.J. and Walker R.F. 1985. Influence of serotonin on the immune response. Immunology. 54: 505-512.

Janowsky, D.S., Risch, S.C. and Ziegler, M.G. 1986. Physostigmine-induced epinephrine release in patients with affective disorder. American Journal of Psychiatry. 143: 919-921.

Jayson, M.I.V., Keegan, A., Million, R. and Tomlinson, I. 1984. A fibrinolytic defect in chronic low back pain syndrome. Lancet. 2:1186.

Jensen, M.P., Karoly, P. and Braver, S. 1986. The measurement of clinical pain intensity: A comparison of six methods. Pain. 27:117-126.

Jessel, T.M. 1985. Cellular interactions at the central and peripheral terminals of primary sensory neurons. Journal of Immunology. 135(suppl): 746-49.

Johnson, R.J. 1981. Vertebrogenic automatic dysfunction-subjective symptoms: A prospective study. Journal of the Canadian Chiropractic Association. 25: 51-57.

Johnson, M.R., Schultz, M.K. and Ferguson, A.C. 1989. A Comparison of chiropractic, medical and osteopathic care for work-related sprains and strains. Journal of Manipulative and Physiological Therapeutics. 12(5): 335-344.

Kirkaldy-Willis, W.H., Burton, C.V. and Cassidy, J.D. 1992. The site and nature of the lesion. In Kirkaldy-Willis, W.H. ed. Managing low back pain. 3rd ed. New York: Churchill Livingstone Inc. 419p. ISBN 0-443-08789-X.

Kirkaldy-Willis, W.H. 1988. Managing low back pain. 2nd ed. New York: Churchill Livingstone Inc. 402p. ISBN 0-443-08535-8.

Korr, I.M. 1975. Proprioceptors and the behaviour of lesioned segments. In Stark. E.H. (ed). Osteopathic Medicine. Acton, MA: Publications Sciences Group. 327p.

Korr, I.M. 1979. The spinal cord as organizer of disease processes: III. Hyperactivity of sympathetic innervation as a common factor in disease. Journal of American Osteopathic Association. 79:232-237.

Korr, I.M. 1986. Somatic dysfunction, osteopathic manipulative treatment, and the nervous system: a few facts, some theories, many questions. Journal of Americal Osteopathic Association. 86: 109 - 114.

Korr, I.M., Denslow, J.S. and Krens, A.D. 1947. Quantitive studies of chronic facilitation in human motoneuron pools. American Journal of Physiology. 150: 229-258.

Lanier, L.L., Phillips, J.H., Hackett, J., Tutt, M., Kumar, V. 1986. Natural killer cells: Definition of a cell type rather than a function. Journal of Immunology. 137:2735.

Leach, R.A. 1994. Neurodystrophic hypothesis. In: The chiropractic theories: A synopsis of scientific research. 3rd ed. Baltimore: Williams and Wilkins. 369p.

Levine, J.D., Moskowitz, M.A. and Basbaum, A.I. 1985. The contribution of neurogenic inflammation in experimental arthritis. Journal of Immunology. 135(suppl): 843-47.

Lewin, T., Moffet, B., Vüdek, A. 1962. The morphology of the lumbar synovial intervertebral joints. Acta Morphology Neerland-Scandanavia. 4:299.

Lohr, G.E., O'Brien, J.C., Nodine, D.L., Brennan, P.C. 1990. Natural killer cells as an outcome measure of chiropractic treatment efficacy. In: Proceedings in the International Conference on Spinal Manipulation. Arlington, Virginia: Foundation for Chiropractic Education and Research.

Lundberg, J.M., Anggard, A. and Pernow, J. 1985. Neuropeptides Y-, substance P- and VIP-immunoreactive nerves in cat spleen in relation to autonomic vascular and volume control. Cell Tissue Research. 239: 9-18.

Magee, D.J. 1992. Orthopedic Physical Assessment. 2nd ed. Philadelphia: WB. Saunders Company. 655p. ISBN: 0-7216-4344-2.

Meade. T.W., Dyer, S., Browne, W., Townsend, J. and Frank A.O. 1990. Low back pain of mechanical origin: Randomized comparison of chiropractic and hospital outpatient treatment. British Medical Journal. 300: 1431-37.

Meade. T.W., Dyer, S., Browne, W., and Frank A.O. 1995. Randomized comparison of chiropractic and hospital outpatient management for low back pain: results from extended follow-up. British Medical Journal. 311: 349-351.

Melzack, R. 1987. The short-form McGill Pain Questionnaire. Pain. 30: 191-197

Mennel, J.M. 1964. Joint pain: Diagnosis and Treatment using Manipulative Techniques. Boston: Little, Brown and Company. 178p. ISBN: 64-14259.

Mullbacher, A., Parish, C. R., Mundy, J. P. 1984. An improved colorimetric assay for T cell cytotoxicity *in vitro*. Journal of Immunological Methods, 68, 205-215.

Munck, A., Guyre, P.M. and Hoolbrook, N.J. 1984. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocrine Review. 5: 25-44.

Nachemson, A.L. 1976. The lumbar spine: an orthopaedic challenge. Spine. 1(1): 59-71.

Ottaway, C.A. 1984. In vitro alteration of receptors for vasoactive intestinal peptide changes the in vivo localization of mouse T cells. Journal Experimental Medicine. 160: 1054-69.

Ottaway, C.A. and Greenberg, G.R. 1984. Interaction of vasoactive intestinal peptide with mouse lymphocytes: specific binding and the modulation of mitogen responses. Journal Immunology. 132:417-22.

Palmer, D.D. 1910. The chiropractor's adjuster: The Science, Art and Philosophy of Chiropractic. Portland, OR, Portland Printing House. p. 119.

Paquet, N., Malouin, F. and Richards, C.I. 1994. Hip-spine movement interaction and muscle activation patterns during sagittal trunk movements in low back pain patients. Spine. 19(5):596.

Payan, D.G. and Brewster, D.R. 1983. Specific stimulation of human T lymphocytes by substance P. Journal of Immunology. 131:1613-15.

Payan, D.G. and Goetzl, E.J. 1985. Modulation of lymphocyte function by sensory neuropeptides. Journal of Immunology. 135(suppl):783-786.

Pernow, B. 1985. Role of tachykinins in neurogenic inflammation. Journal of Immunology. 135(suppl): 812-15.

Phipps, R.P., Stein, S.H., Roper, R.L. 1991. A new view of prostaglandin E regulation of the immune response. Immunology Today. 12:349-51.

Pope, M.H., Phillips, R.B., Haugh, L.D., Hsieh, C.Y., MacDonald, L., and Haldeman, S. 1994. A prospective, randomized three week trial of spinal manipulation, transcutaneous muscle stimulation, massage and corset in the treatment of subacute low back pain. Spine, 19(22): 2571-7.

Rahlmann, J.F. 1987. Mechanisms of intervertebral joint fixation: A literature review. Journal of Manipulative and Physiological Therapeutics. 10(4): 127-134.

Reichert, T., DeBruyere, M. Deneys, V. 1991. Lymphocyte subset reference ranges in adult Caucasians. Clinical Immunology and Immunopathology. 60: 190-208.

Renz, H., Gong, J.H., Schmidt, A., Nain, M. and Gemsa, D. 1988. Release of tumor necrosis factor-a from macrophages. Enhancement of suppression are dose-dependently regulated by prostaglandin E2 and cyclic nucleotides. Journal of Immunology. 141:2388-93.

Sanders, V.M. and Munson, A.E. 1985. Norepinephrine and the antibody response. Pharmacology Review. 27:229-248.

Sandoz, R. 1976. Some physical mechanisms and effects of spinal adjustments. Annals of the Swiss Chiropractic Association. 6:91-141.

Sato, A., Swenson, R.S. 1984. Sympathetic nervous system response to mechanical stress of the spinal column in rats. Journal of Manipulative Physiological Therapeutics. 7: 141-147.

Schafer, R.C. and Faye, L.J. 1989. Motion Palpation and Chiropractic Technique. 2nd ed. Motion Palpation Institute. 426p.

Shekelle, P.G., Adams, A.H., Chassin, M.R., Hurwitz, E.L. and Brook, R.H. 1992. Spinal manipulation for low back pain. Annals of Internal Medicine. 117: 590-598.

Sims-Williams, H., Jayson, M.I.V., Young, S.M.S., Baddeley, H. and Collins, E. 1979. Controlled trial of mobilisation and manipulation for low back pain: hospital patients. British Medical Journal. 2: 1138-1140.

Spector, N.H. 1987. Anatomic and physiologic connections between the central nervous and the immune systems. Reprinted in Research Forum. pp 103-17.

Stano, M. 1993. A comparison of health care costs for chiropractic and medical patients. Journal of Manipulative and Physiological Therapeutics. 16(5) 291-299.

Sternberg, E.M., Wedner, H.J. and Leung, M.K. 1986. Effect of serotonin (5-HT) and other monoamines on murine macrophages: suppression in Ia expression by serotonin. Journal of Immunology. 137: 276-281.

Szaraz, Z.T. 1990. Compendium of Chiropractic Technique. 2nd ed. Toronto: Vivian L.R. Associates Ltd. Technical Publications. 92p.

Sunderland, S. 1978. Traumatized nerves, roots, and ganglia: musculo-skeletal factors and neuropathological consequences. In: Korr I .M. (ed). The Neurobiologic

Mechanisms in Manipulative Therapy. New York, Plenum. 466p. ISBN. 0-306-31150X.

Terret, A.C.J. and Vernon, H. 1984. Manipulation and pain tolerance: A controlled study of the effect of spinal manipulation on paraspinal cutaneous pain tolerance levels. American Journal of Physical Medicine. 63(5): 217-225.

Timonen, T., Ortaldo, J., Herberman, R.B. 1981. Characteristics of human large granular lymphocytes and relationship to natural killer and K cells. Journal of Experimental Medicine. 153:569.

Triano, J.J. 1995. Manipulative therapy versus education programs in chronic low back pain. Spine. 20: 948-955.

Vernon, H. 1996. Spinal manipulation for chronic low back pain: a review of the evidence. Journal of the Canadian Chiropractic Association. 40(3): 180-182.

Vernon, H.T., Dhami, M.S.I., Howley, T.P. and Annet R. 1986. Spinal manipulation and β-endorphin: a controlled study of the effects of a spinal manipulation on plasma β-endorphin levels in normal males. Jounal of Manipulative and Physiological Therapeutics. 9:1-4.

Vora, G., Bates, H. 1980. The effects of spinal manipulation on the immune system. American Chiropractic Association Journal of Chiropractic. 14(Oct): S103-5.

Waagen, G.N., Haldeman, S., Cook, G., Lopez, D. And De Boer, K.F. 1986. Short-term trial of chiropractic treatment for the relief of chronic low back pain. Manual Medicine. 2:63-67.

Wall, P.D. 1978. The gate control theory of pain mechanisms: a re-examination and re-statement. Brain. 101:1-18.

Weinstein, J.N., Claverie, W. and Gibson, S. 1988. The pain of discography. Spine. 13: 1344-1348.

Weinstein, J.N., Pope, M., Schmidt, R. and Seroussi, R. 1988. Neuropharmacologic effects of vibration on the dorsal root ganglion. An animal model. Spine. 13(5): 521-525.

Weinstein, J.N. 1991. Anatomy and neurophysiologic mechanisms of spinal pain. In Frymoyer, J.W. (Ed). The Adult Spine: Principles and Practice. New York: Raven Press, Ltd. 2178p. ISBN: 0-88167-689-6. (set).

Whiteside, T.L. and Herberman, R.B. 1989. The role of natural killer cells in human disease: Short analytical review. Clinical Immunology and Immunopathology. 53: 1-23.