EVALUATION OF N-ACETYLCYSTEINE AND VITAMIN "E" IN PROPHYLAXIS AND TREATMENT OF NEUROTOXICITY INDUCED BY "2, 5-HEXANEDIONE"

THESIS

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وَمَا أُوتِيتُم مِنَ العِلمِ إِلَّا قَلِيلًا

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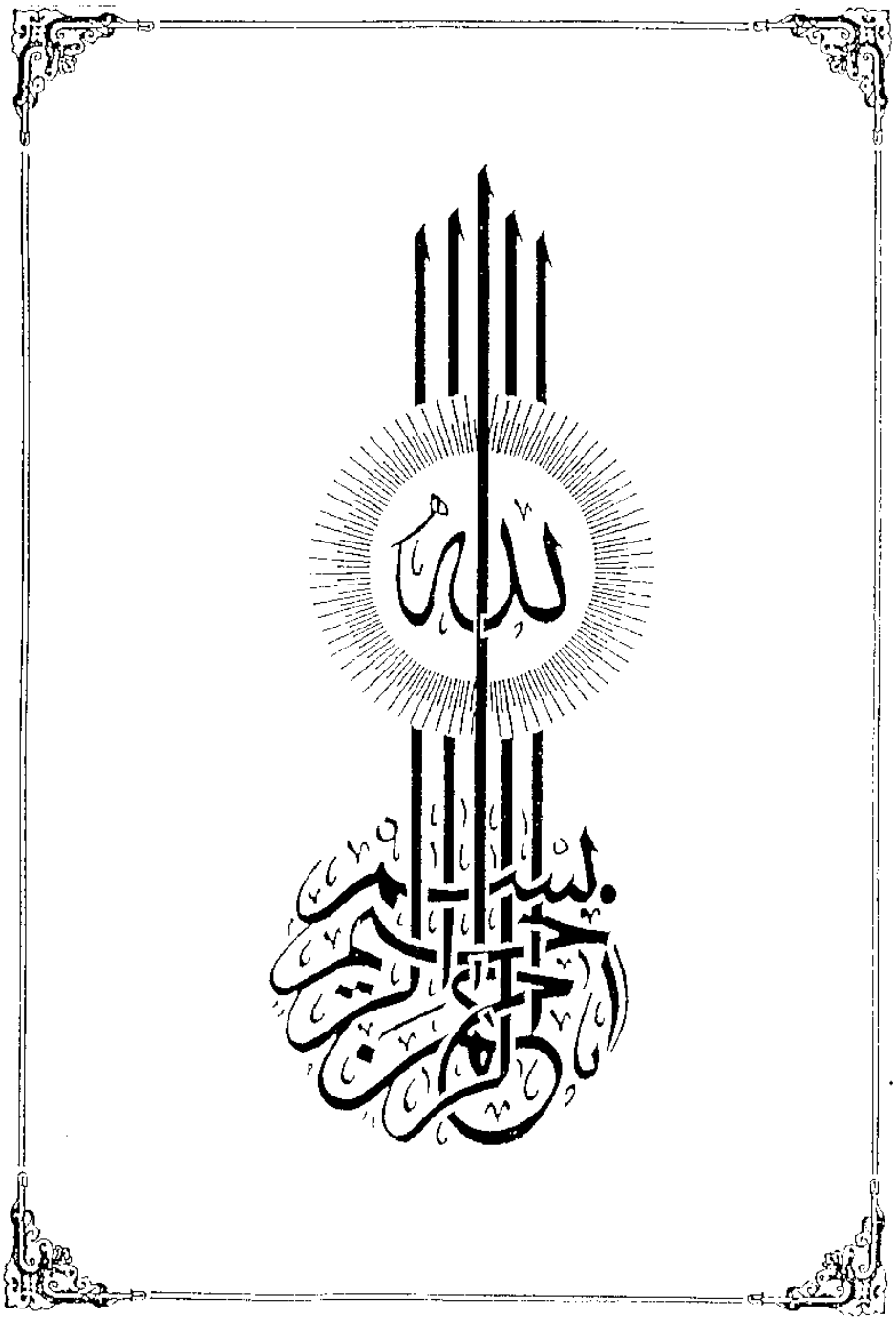

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TO MY PARENTS

TO MY BELOVED WIFE

TO MY SWEETHEART AHMED

AND USAMA . . . . . .

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LIST OF ABBREVIATIONS

n-Hx	n-Hexane
2,5-HD	2,5-Hexanedione
2,5-HDiol	2,5-Hexanediol
MEK	Methyl ethyl ketone
Mn-Bk	Methyl n-butyl ketone
IDPN	B,B-iminodipropionitrile(neurotoxic compound)
NAC	N-Acetylcysteine
IF(s)	Intermediate filament(s)
NF(s)	Neurofilament(s)
NFP(s)	Neurofilament protein(s)
NFL, NFM, NFH	Neurofilament, low, medium and high respectively
Mt	Microtubules
MAP(s)	Microtubule associated protein(s)
Sca	Slow component$_{\alpha}$ of axonal transport
OSHA	Occupational Safety and Health Administration
ACGIA	American Conference of Governmental Industrial Hygienists
U.S. DHEW	United States Department of Health Education and Welfare
TLV(s)	Threshold Limit Value(s)

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TLV-TWA	Threshold Limit Value-Time Weighted Average
LD_{50}	Lethal $dose_{50}$
NCV	Nerve Conduction Velocity
NAP	Nerve Action Potential
MAP	Muscle Action Potential
GSH	Reduced glutathione
GSSG	Oxidized glutathione
LFB	Luxol Fast Blue
DTT	Dithioreitol (sulfhydryl donor)
GAPDH	Glyceraldehyde 3 - phosphate dehydrogenase
PFK	Phosphofructokinase
GSSG-R	Glutathione reductase
GSH-PX	Glutathione peroxidase
SOD	Superoxide dismutase
XOD	Xanthine Oxidase
SDS-PAGE	Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis
ANOVA	Analysis of Variance

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CONTENTS

Page

* INTRODUCTION 1
* HISTORICAL REVIEW 3
* ANATOMICAL PRINCIPLES 5
  The Neurone 5
  Neuronal CytoSkeleton 7
  Neurofilaments 9
  Axonal Transport 12
* NEUROTOXIC HEXACARBONS 14
  - N- Hexane 14
  - 2, 5-Hexanedione 15
  - Methy n-butyl Ketone 16
* TOXICOLOGY OF NEUROTOXIC HEAXACARBONS 17
* PHARMACOKINETICS AND BIOTRANSFORMATION OF NEUROTOXIC HEXACARTONS 19
* HUMAN HEXACARBON TOXICITY 24
  - Sources of Human Exposure 24
  - Effects of Acute Human Exposure 25
  - Effects of Subacute and Subchronic Exporure 25
    Clinical picture 25
    Electrophysiological studies in man 28
    Laboratory findings 29
    Neuropathological findings 29
    Diagnosis 30
    Defferential diagnosis 30

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* **EXPERIMENTAL TOXICOLOGY OF HEXACARBONS** 31

Effects of Repetitive or Continuous Exposure 31

- General changes 31

- Body weight 31

- Behavioral changes 32

- Electrophysiological studies 32

- Functional sings 33

- Neuropathological findings 33

- Therapentic trials 38

* **PATHOGENESIS OF HEXACARBON NEUROPATHY**

* **STRUCTURE ACTIVITY RELATINSHIPS** 39

* **THEORIES OF HEXACARBON NEUROPATHY** 40

A - Interruption of Energy Metabolison 40

B - Inhibition of Sterologenesis 43

C - Disruption of Neurofilaments 43

D - Inhibition of Normal Turnover of Neurofilaments 49

* **N-ACETYLCYSTEINE** 50

* **VITAMIN E** 53

* **METHODOLOGY** 61

- Experimental Animals 61

- Feeding 61

- Chemicals 61

- Animal Treatment Protocol 62

- Experimental Parameters 63

Body weight changes 64

Water intake and dosage of 2 5-HD 64

Clinical neurological evaluation 64

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Assessment of neurobehavioural function 65
Animals survival..... 69
Sacrifice of the animals..... 69
Histopathlogy..... 70
Enzymes assay..... 72
Gutathione reduactase..... 73
Glutathione peroxidase..... 74
Superoxide dismutase..... 76
Preparation of the spinal cord cytoskeleton 77
Separation of neurofilament proteins..... 78
The electrophoretic run..... 82
Electrotransfer and immunobinding..... 90
Statistical Analysis..... 94
* **RESULTS DISCUSSION AND CONCLUSION**.....
* **ROLE OF N-ACETYLCYSTEINE**..... 96
- Role of N-Acetylcysteine in Prevention and Treatment of 2,5-HD Neurotoxicity..... 96
Results..... 96
Dicussion 124
- Effect of N-acetycysteine on recovery of2,5-HD neurotoxicity..... 130
Results..... 130
Discussion..... 136
Conclusion..... 137
* **ROLE OF VITAMIN E**..... 138
- Role of Vitamin E in Prevention and Treatment of 2,5-HD Neurotoxicity.....

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Results..... 138
Discussion..... 153
Effect of Vitamin E on Recovery of 2,5-HD Neuro-
toxicity..... 155
Results..... 155
Discussion..... 162
Conclusion..... 163
MARY..... 164
ERENCES..... 171
BIC SUMMARY

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INTRODUCTION

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INTRODUCTION

As a result of industrial exposure (Herskowitz et al., 1971) or deliberate inhalation of glues containing hexacarbon solvents (Goto et al., 1974), hexacarbon neurotoxicity is a world-wide problem. Numerous cases of hexacarbon-induced neuropathy have been reported in Italy (Abbritti et al., 1976; Battistini et al., 1974).,Japan (Yamamura, 1969), Morrocco (Cavignaux, 1972), France (Gaultier et al, 1973), and the United States (Mendell et al., 1974; Allen, 1975, Allen et al., 1975). A similar clinical neuropathy is readily produced in experimental animals (Mendell et al., 1974; Spencer et al., 1978). This syndrome is characterized by degeneration of long-central and peripheral myelinated nerve fibers, resulting in eventual neuromuscular paralysis and sensory alterations (Schaumburg and Spencer, 1976).

It is important to study hexacarbon-induced neurotoxicity not only because of the great potential for human exposure to these solvents, but also, because of the possibility of demonstrating a common mechanism of action of these and other chemicals causing a similar neuropathy.

This study examined the roles of N-acetyl-cysteine and Vitamin E in preventing, treating, and or enhancing recovery of hexacarbon-induced axonopathies.

In addition to the therapeutic benefit, identification of substances that may block or modify the neurotoxic response to hexacarbon compounds might provide clues to the biochemical mechanisms underlying distal axonopathy.

Although the use of 2,5-hexanedione (2,5-HD) in industry is rather restricted, it has been employed as an experimental model of this neuropathy (Spencer and Schaumburg, 1975, 1976) because it is recognized as the ultimate toxic metabolite of the most commonly used neurotoxic hexacarbon compounds in several species, including man (Krasavage et al., 1980). It was selected also

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because it is completely soluble in water and can be administered by the oral route (simple) to produce a neurotoxicity identical to that produced by exposure to other hexacarbons (Spencer and Schaumburg, 1975).

Rats were employed because they metabolize the hexacarbons like man and 2,5-HD has the same effect on them as on human (Gilbert and Maurissen, 1982).

In an attempt to participate in the debate regarding the molecular pathogenesis of hexacarbon-induced central-peripheral-distal axonopathy, the tested therapeutic compounds were scrutinized for their effect on neurobehavior, on indogenous protective antioxidant enzyme systems, and on the cytoskeleton of the tested rats.

Employment of N-acetyl-cysteine as a therapeutic agent grew out of the theories proposed by Sabri et al. (1979a) implicating inhibition of sulfhydryl containing glycolytic enzymes as the underlying biochemical lesion for hexacarbon neuropathy.

The popularity of the theory regarding pyrrole adduct formation and autoxidation as an essential step in the pathogenesis of hexacarbon neuropathy provided the impetus for selecting Vitamin E (antioxidant). Another reason for this was the work done by Rosenberg et al. (1987b) which demonstrated exaggeration of hexacarbon (2,5-hexanedione) neurotoxicity by hyperbaric oxygen in rats.

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