

# LABORATORY MONITORING OF CADMIUM-INDUCED NEPHROTOXICITY

*Thesis Submitted for the Partial Fulfillment of the M.D. Degree in  
Chemical and Clinical Pathology*

By

**Sayed Abd El-Rahim Saleh**

M.B., B.Ch.

M.Sc. in Chemical and Clinical Pathology

Supervised by

**Prof. Dr. Mahmoud Sabry Sallam**

Professor of Chemical and Clinical Pathology

**Prof. Dr. Sawzan Said Hafez**

Professor of Chemical and Clinical Pathology

**Dr. Ola Hamdy Demerdash**

Assistant Professor of Chemical and Clinical Pathology

**Dr. Arig Ali Mahmoud Seif**

Lecturer of Chemical and Clinical Pathology

Faculty of Medicine

Ain Shams University

1998

Nadia Abdel  
Sattar

the 1990s, the number of people with a mental health problem has increased by 50% (Mental Health Foundation 1999). The prevalence of mental health problems in the UK is estimated to be 10% (Mental Health Foundation 1999).

There is a growing awareness of the need to address the needs of people with mental health problems in the workplace. The Department of Health (1999) has published a strategy for mental health care, which includes a commitment to 'improve the lives of people with mental health problems by ensuring that they are able to participate fully in society and the workplace'. The strategy also states that 'the workplace should be a place where people with mental health problems can thrive and contribute to the economy'.

There is a growing awareness of the need to address the needs of people with mental health problems in the workplace. The Department of Health (1999) has published a strategy for mental health care, which includes a commitment to 'improve the lives of people with mental health problems by ensuring that they are able to participate fully in society and the workplace'. The strategy also states that 'the workplace should be a place where people with mental health problems can thrive and contribute to the economy'.

There is a growing awareness of the need to address the needs of people with mental health problems in the workplace. The Department of Health (1999) has published a strategy for mental health care, which includes a commitment to 'improve the lives of people with mental health problems by ensuring that they are able to participate fully in society and the workplace'. The strategy also states that 'the workplace should be a place where people with mental health problems can thrive and contribute to the economy'.

There is a growing awareness of the need to address the needs of people with mental health problems in the workplace. The Department of Health (1999) has published a strategy for mental health care, which includes a commitment to 'improve the lives of people with mental health problems by ensuring that they are able to participate fully in society and the workplace'. The strategy also states that 'the workplace should be a place where people with mental health problems can thrive and contribute to the economy'.

There is a growing awareness of the need to address the needs of people with mental health problems in the workplace. The Department of Health (1999) has published a strategy for mental health care, which includes a commitment to 'improve the lives of people with mental health problems by ensuring that they are able to participate fully in society and the workplace'. The strategy also states that 'the workplace should be a place where people with mental health problems can thrive and contribute to the economy'.

There is a growing awareness of the need to address the needs of people with mental health problems in the workplace. The Department of Health (1999) has published a strategy for mental health care, which includes a commitment to 'improve the lives of people with mental health problems by ensuring that they are able to participate fully in society and the workplace'. The strategy also states that 'the workplace should be a place where people with mental health problems can thrive and contribute to the economy'.

There is a growing awareness of the need to address the needs of people with mental health problems in the workplace. The Department of Health (1999) has published a strategy for mental health care, which includes a commitment to 'improve the lives of people with mental health problems by ensuring that they are able to participate fully in society and the workplace'. The strategy also states that 'the workplace should be a place where people with mental health problems can thrive and contribute to the economy'.



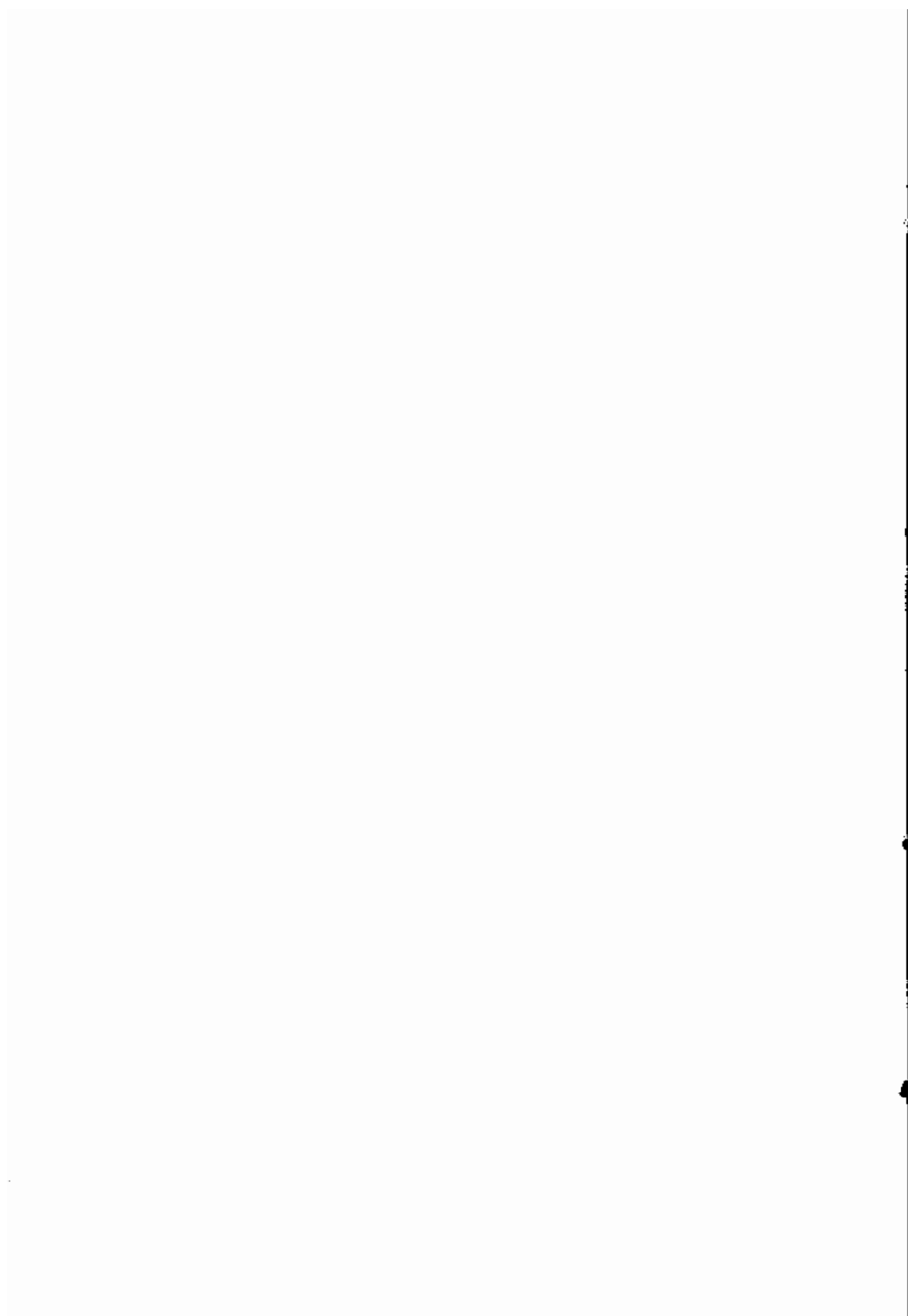
بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

**قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا،**

**إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ**

صدق الله العظيم

سورة البقرة- الآية: ٣٢



## *ACKNOWLEDGMENT*

*I would like to express my deepest gratitude to Prof. Dr. Mahmoud Sabry Sallam, Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University for giving me the honor to work under his supervision. He generously offered me a great help through his experience, support and encouragement.*

*My sincere appreciation to Prof. Dr. Sawzan Said Hafez, Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University, for her generous cooperation, continuous advice and support, which made the completion of this work possible.*

*I am deeply indebted to Dr. Ola Hamdy Demerdash, Assistant Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University, for extreme patience, keen supervision. She offered me great help and valuable discussion that attended every stage in this work.*

*I am also grateful to Dr. Arig Ali Seif, Lecturer of Clinical Pathology, Faculty of Medicine, Ain Shams University, for her honest assistance and precious guidance. She offered me a lot of time and effort throughout the whole work.*

*Finally, my deepest thanks to my family and my colleagues for their good help received in many ways.*

*Sayed Abdel-Rahim*



## LIST OF CONTENTS

	Page
<b>INTRODUCTION AND AIM OF THE WORK</b>	<b>1</b>
<b>REVIEW OF LITERATURE</b>	<b>3</b>
<b>I. CADMIUM</b>	<b>3</b>
A. Sources of Cadmium	3
B. Physical and Chemical Properties	4
C. Uses of Cadmium	5
1. Electroplating	5
2. Alloys	5
3. Nuclear Reactors	5
4. Pigments	5
5. Phosphate Fertilizers	5
D. Sources of Exposure	6
1. Industrial Sources	6
2. Non-Industrial Sources	6
E. Cadmium Metabolism	11
1. Absorption	11
2. Distribution	12
3. Excretion	14
F. Methods of Assay of Cadmium	16
1. Types of Samples	16
2. Specimen Collection and Storage	16
3. Methods of Quantitative Cadmium Determination:	18
a. Atomic absorption spectrometry (AAS)	18
b. Electrochemical Methods	19
c. Activation analysis	21
d. In vivo method	21
<b>II. HEALTH EFFECTS OF CADMIUM</b>	<b>22</b>
A. Acute Cadmium Poisoning	22
1. Industrial Poisoning	22
2. Non-Industrial Poisoning	22
B. Chronic Cadmium Poisoning	23
1. Chronic Pulmonary Diseases	23
2. Chronic Renal Diseases	24
• Role of metallothionein in cadmium-induced nephrotoxicity	27
3. Bone Diseases	29
4. Hypertension and Cardiovascular Diseases	30
5. Carcinogenicity	30
6. Liver Diseases	31
7. Other Effects	31



<b>III. MONITORING OF EARLY NEPHROTOXIC EFFECTS</b>	<b>32</b>
<b>OF CADMIUM</b>	<b>32</b>
<b>PROTEINURIA:</b>	<b>32</b>
A. Glomerular Proteinuria	33
1. Pathogenesis of Microalbuminuria in Cadmium Toxicity	33
2. Laboratory Assessment of Microalbuminuria	34
a. Type of urine sample	34
b. Storage condition	34
c. Methods of assay of microalbuminuria	34
(i) Latex agglutination test	34
(ii) Micral test strips	35
(iii) Immunoturbidimetry	35
(iv) Laser immunonephelometry	35
(v) Radial immunodiffusion	35
(vi) Enzyme linked immunosorbent assay	36
(vii) Radioimmunoassay	36
B. Tubular Proteinuria	36
• Alpha-1-Microglobulin	37
1. Structure	37
2. Synthesis of alpha-1-microglobulin	38
3. Distribution	38
4. Renal handling of alpha-1-microglobulin	38
5. Pathological variations in serum, urinary alpha-1-microglobulin levels	39
(a) Alpha-1-microglobulin in hepatic diseases	39
(b) Alpha-1-microglobulin in renal diseases	39
(c) Alpha-1-microglobulin in other diseases	40
6. Laboratory assessment of alpha-1-microglobulin level:	40
(a) Specimen collection and storage	40
(b) Analytical methods of alpha-1-microglobulin	40
(i) Latex agglutination test	40
(ii) Nephelometric immunoassay	41
(iii) Single radial immunodiffusion	41
(iv) Enzyme linked immunosorbent assay	41
(v) Radioimmunoassay	42
<b>SUBJECTS AND METHODS</b>	<b>43</b>
<b>I. SUBJECTS</b>	<b>43</b>
<b>II. SAMPLES</b>	<b>45</b>
A. Blood Samples	45
B. Urine Samples	45
<b>III. METHODS</b>	<b>46</b>
A. Assessment of Serum Glucose, Liver and Kidney Function Tests	46
1. Glucose	46
2. Urea	46
3. Creatinine	47
4. Uric Acid	47

5. Total Bilirubin	48
6. Aspartate Aminotransferase	48
7. Alanine Aminotransferase	49
8. Alkaline Phosphatase	49
9. $\gamma$ -glutamyl Transferase	50
10. Total Proteins	50
11. Albumin	50
B. Determination of Cadmium	51
C. Determination of Alpha-1-Microglobulin	53
D. Determination of Microalbumin	55
<b>IV. STATISTICAL METHODS:</b>	<b>56</b>
A. Basic Mathematical Relations	56
B. Tests of Significance	56
C. Correlation Study	57
D. Evaluation of Diagnostic Sensitivity of Alpha-1-microglobulin and microalbumin	58
<b>RESULTS</b>	<b>59</b>
<b>DISCUSSION</b>	<b>90</b>
<b>SUMMARY</b>	<b>96</b>
<b>CONCLUSION AND RECOMMENDATIONS</b>	<b>98</b>
<b>REFERENCES</b>	<b>99</b>
<b>ARABIC SUMMARY</b>	



## LIST OF ABBREVIATIONS

A-1-M:	Alpha-1-microglobulin
AAS:	Atomic absorption spectrometry
ACGIH:	American Conference of Governmental Industrial Hygienists
ADP:	Adenosine diphosphate
ALP:	Alkaline phosphatase
Alpha-1-M:	Alpha-1-microglobulin
ALT:	Alanine amino transferase
AMP:	2-amino-methyl-1-propanol
AST:	Aspartate amino transferase
ATP:	Adenosine triphosphate
ATPase:	Adenosine triphosphatase
BCP:	Bromocresol purple
BUN:	Blood urea nitrogen
Cd (CO <sub>3</sub> ) <sub>2</sub> :	Cadmium carbonate
Cd-Mt:	Cadmium-metallothionein
Cd-U:	Urinary cadmium
Cd:	Cadmium
CdCl <sub>2</sub> :	Cadmium chloride
CdO:	Cadmium oxide
CdS:	Cadmium sulfide
COPD:	Chronic obstructive pulmonary diseases
DCHBS:	3,5-dichloro-2-hydroxybenzene sulfonate
DPASV:	Differential pulse anodic stripping voltammetry
EIA:	Enzyme immunoassay
ELISA:	Enzyme linked immunosorbent assay
ETA:	Electrothermal atomization
ETAA:	Electrothermal atomic absorption
FN:	False negative
G6PDH:	Glucose-6-phosphate dehydrogenase
GFR:	Glomerular filtration rate
GGT:	$\gamma$ -glutamyl transferase
GLDH:	Glutamate dehydrogenase
H <sub>2</sub> O <sub>2</sub> :	Hydrogen peroxide
HBB:	High body burden
HC-albumin:	Alpha-1M albumin
HC-IgA:	Alpha-1-M-IgA
HK:	Hexokinase
IAP:	Intestinal alkaline phosphatase
LAT:	Latex agglutination test
LBB:	Low body burden
LDH:	Lactate dehydrogenase

LMW:	Low molecular weight
MA:	Microalbumin
MBB:	Moderate body burden
MDH:	Malate dehydrogenase
Mt:	Metallothionein
NAD:	Nicotinamide adenine dinucleotide
NADH:	Nicotinamide adenine dinucleotide dehydrogenase
NAG:	N-acetyl- $\beta$ -glucosaminidase
NHO <sub>3</sub> :	Nitric acid
NIOSH:	National Institute for Occupational Safety and Health
PAM:	Pulmonary alveolar macrophage
pI:	Isoelectric point
PIXE:	Proton induced X-ray emission
Protein HC:	Human complex forming glycoprotein
RBP:	Retinol binding protein
RIA:	Radioimmunoassay
RID:	Radial immunodiffusion
SRID:	Single radial immunodiffusion
TP:	True positive
VLC:	Very low concentration
WHO:	World Health Organization
$\beta_2m$ :	Beta2 microglobulin

## LIST OF TABLES

	Page
• Table (1): Major toxic agents in the gas phase of cigarette smoke	7
• Table (2): Major toxic agents in the particulate matter of cigarette smoke	8
• Table (3): Data of control group (Gp C)	66
• Table (4): Data of Cadmium exposed workers (Gp I)	67
• Table (5): Data of smokers group (Gp II)	68
• Table (6): Descriptive statistics of urinary cadmium (Cd-U), alpha-1-microglobulin (alpha-1-M) and microalbumin (MA) in exposed workers (Gp I), smokers group (Gp II) and control group (Gp C).	69
• Table (7): Statistical comparison between urinary cadmium (Cd-U), alpha-1-microglobulin (alpha-1-M), microalbumin (MA) levels of the various studied groups using logistic t test.	69
• Table (8): Descriptive statistics of urinary cadmium (Cd-U), alpha-1-microglobulin (alpha-1-M) and microalbumin (MA) in exposed workers (Gp I) according to the duration of exposure.	70
• Table (9): Statistical comparison between urinary cadmium (Cd-U), alpha-1-microglobulin (alpha-1-M), microalbumin (MA) levels in exposed workers (Gp I) after different periods of exposure as compared to the control group (Gp C) and to each other using logistic t test.	71
• Table (10): Descriptive statistics of alpha-1-microglobulin (alpha-1-M) and microalbumin (MA) in exposed workers with different urinary cadmium levels.	72
• Table (11): Statistical comparison between alpha-1-microglobulin (alpha-1-M), microalbumin (MA) levels in exposed workers (Gp I) at different cadmium levels as compared to the control group (Gp C) and to each other using logistic t test.	73
• Table (12): Descriptive statistics of urinary cadmium (Cd-U), alpha-1-microglobulin (alpha-1-M) and microalbumin (MA) in smokers group (Gp II) according to the duration of smoking.	74
• Table (13): Statistical comparison between urinary cadmium (Cd-U), alpha-1-microglobulin (alpha-1-M), microalbumin (MA) levels in smokers group (Gp II) after different periods of smoking as compared to the control group (Gp C) and to each other using logistic t test.	75
• Table (14): Descriptive statistics of alpha-1-microglobulin (alpha-1-M) and microalbumin (MA) levels in smokers group (Gp II) with different urinary cadmium levels.	76
• Table (15): Statistical comparison between alpha-1-microglobulin (alpha-1-M), microalbumin (MA) levels in smokers group (Gp II) at different cadmium levels as compared to the control group (Gp C) and to each other using logistic t test.	77
• Table (16): Statistical comparison between urinary cadmium levels of workers and smokers of the same period of exposure using logistic t test.	78
• Table (17): Correlation study between various studied parameters in exposed workers (Gp I) and smokers (Gp II) using Spearman's rank correlation coefficient.	79

