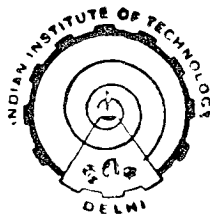


LEAD TOXICITY AND ITS BIOLOGICAL CORRELATES

by

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THESIS SUBMITTED TO THE
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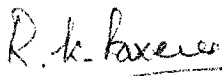


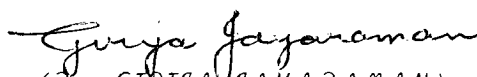
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CERTIFICATE

This is to certify that the thesis entitled "LEAD TOXICITY AND ITS BIOLOGICAL CORRELATES" being submitted by NIVEDITA KARMAKAR for the award of the degree of DOCTOR OF PHILOSOPHY, is a record of the original bonafide research work carried out by her. She has worked under our joint guidance and supervision and has fulfilled the requirements for the submission of this thesis. The results presented in this thesis have not been submitted in part or full to any other University or Institute for award of any degree/diploma.


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PREFACE

The occurrence of lead in our environment is ubiquitous. It occurs both as a natural element as well as a pollutant from different sources - smelter emission, effluent from industry and automobile exhaust. The toxic effects of overdoses of lead were recognised since ancient times. The problem of lead as an occupational, industrial and environmental hazard is one of the main concerns in the present day society. Various aspects of the problem have been researched extensively and the toxicology of lead is well documented, but despite all this work, many physiological actions of lead are not well understood. The work in this thesis has been undertaken with the object of elucidating some of the effects of lead on the digestive and hematopoietic systems through experimental lead poisoning. The intestinal absorption and retention is the major pathway for lead intake. About 40% of the inhaled lead is trapped in the upper respiratory tract and swallowed. Most of the clinical symptoms of lead intoxication arise as a result of ingested lead. The process of ingestion therefore, is an important means of lead toxicity and so the mode of oral administration of inorganic lead to rats has been selected.

Chapter 1 is a brief review of the current status of studies done on lead intoxication. The partitioning of lead among target organs and the concentration of diffusible lead

in the soft tissues are directly responsible for toxic symptoms. The toxicity is manifested in different areas of physiologic functions. Chapter II elaborates on the hematological and rheological studies done with blood obtained from lead exposed rats. These parameters are likely to affect the viscosity of blood. The latter plays an important role in the mechanics of transport of blood and also in diffusion across the red cell membrane. However, investigation of change in viscosity of blood, in the light of toxic manifestations of lead on red blood corpuscles, has not been reported so far. Along with reduction in hemoglobin concentration, hematocrit and red blood cells, we have observed an increase in the apparent viscosity of blood in lead treated rats. The change in viscosity may be a consequence of the structural deformation of red cells which is confirmed by scanning electron microscopic studies.

Chapter III deals with the experimental study of the toxic effect of intestinal uptake of lead acetate on gastrointestinal motility. The motility in the duodenal region has been measured *in vivo* by implanting an electrical impedance probe in that region. It is observed that lead affects the contractile properties of the intestine in rats. The amplitude of contraction in lead treated rats is significantly smaller compared to that of the controls. Transit was also measured using charcoal as the marker and our results indicate quantitatively the effect of inhibition on net transit which is significantly reduced. The gross changes in the intestinal motility have been measured experimentally

as described in Chapter III. However, the determination of actual distribution of the lead ion in the cellular and extracellular phases of intestine, as a function of time, has not been done experimentally. Chapter IV deals with a simple diffusion model of the intestinal wall which describes the transient overall uptake of lead ions across the mucosa and their subsequent uptake in the underlying blood capillaries. The gastrointestinal wall is treated as a heterogeneous two phase medium. The equations predict the intracellular and extracellular concentrations of lead as a function of time. An estimate of the intestinal membrane permeability for lead molecule has been made and it is calculated to be $0.334 \times 10^{-2} \text{ sec}^{-1}$. Finally, the rate of lead uptake by the blood, for different hypothetical gut concentrations has been computed.

Chapter V describes the study of histopathological and ultrastructural alterations induced in the intestine, liver and kidney of rat by oral intake of lead acetate. The functional lesions observed in the small intestine are likely to be related to the structural counterparts. Liver and kidney are the two main detoxifying organs and therefore target systems and hence they were chosen for histological studies. Several degenerative changes were observed in all three organs which were suggestive of the functional lesions. The mitochondria undergo severe material degeneration which indicates that the energy metabolism in the cell is disturbed. In all the three tissues structural damage at the cellular level is found to be enhanced with increasing

lead treatment.

The last few pages outline the conclusions and directions of future work with regard to the investigations made in this study.

CONTENTS

	PAGE
PREFACE	i - iv
CHAPTER I CURRENT TRENDS IN STUDIES OF LEAD TOXICITY	
1.1 Occupational Lead Poisoning	2
1.2 Lead in the Environment	3
1.3 Sources of Ingestion	4
1.4 Relative Risk in Different Populations	5
1.5 Distribution of Lead in the Body	6
1.6 Lead Toxicity in Different Systems	
1.6.1 Nervous system	7
1.6.2 Urinary system	8
1.6.3 Endocrine system	9
1.6.4 Circulatory system	10
1.6.5 Digestive system	12
1.6.6 Gastrointestinal absorption	13
CHAPTER II EFFECT OF LEAD ON THE HEMATOLOGICAL AND RHEOLOGICAL PROPERTIES OF BLOOD	
2.1 Introduction	16
2.2 Materials and Methods	20
2.2.1 Whole blood lead determination	21
2.2.2 Hematological indices	22
2.2.3 Viscosity determination	26
2.2.4 Scanning electron microscopy of erythrocytes	29
2.3 Results	30
2.4 Discussion	33
Summary	39

CHAPTER III EFFECT OF LEAD ON GASTROINTESTINAL MOTILITY

3.1	Introduction	51
3.2	Material and Methods	58
3.2.1	Transducer	59
3.2.2	Animal preparation for measurement of motility	60
3.2.3	Measurement of gastrointestinal transit	61
3.3	Analysis	62
3.4	Results	64
3.5	Discussion	66
	Summary	73

CHAPTER IV ABSORPTION OF LEAD THROUGH THE GASTROINTESTINAL MUCOSA

4.1	Introduction	79
4.2	The Mathematical Model	85
4.3	Results	90
4.4	Discussion	90
	Summary	95

CHAPTER V EFFECT OF LEAD ON THE HISTOPATHOLOGY AND ULTRASTRUCTURE OF THE DUODENUM, LIVER AND KIDNEY

5.1	Introduction	106
5.2	Material and Methods	110
5.2.1	Light microscopy	110
5.2.2	Scanning electron microscopy	110
5.2.3	Transmission electron microscopy	111
5.3	Results	112
5.4	Discussion	115

	PAGE
Summary	118
CONCLUSIONS	126
REFERENCES	129