# HISTOLOGICAL STUDY OF THE EFFECT OF METHOTREXATE ON THE MUCOSA OF THE SMALL INTESTINE IN YOUNG IMMATURE ALBINO RAT WITH SPECIAL REFERENCE TO THE PROTECTIVE ROLE OF VITAMIN A.

**Thesis**

Submitted For Partial Fulfilment Of M.D. Degree In Basic Sciences

**(Histology)**

***By***


**SUZI HANAFY IBRAHIM**

**M.B., B.Ch.-M. Sc.**

*Assistant Lecturer Of Histology*

*Faculty Of Medicine -Ain Shams University*


***Supervised By***


**Prof. Dr. OLFAT S. AHMED**

*Prof. Of Histology*

*Faculty Of Medicine - Ain Shams University*

**Prof. Dr. SAMI H. HAMED**

*Prof. Of Histology*

*Faculty Of Medicine - Ain Shams University*

**Prof. Dr. ELHAM M. GAMAL EL DIN**

*Prof. Of Histology*

*Faculty Of Medicine - Ain Shams University*

**PROF. DR. EZZ EL DIN H. HELAIEL**

*Prof. Of Anatomy*

*Faculty Of Medicine - Ain Shams University*



**Faculty Of Medicine - Ain Shams University**

**1998**



Central Library - Ain Shams University

Central Library - Ain Shams University

بسم الله الرحمن الرحيم

Central Library - Ain Shams University

بسم الله الرحمن الرحيم

Central Library - Ain Shams University

Central Library - Ain Shams University

To

My Family

Central Library - Ain Shams University

Central Library - Ain Shams University

# Acknowledgment

I would like to express my thanks and gratitude to Prof. Dr. Olfat S. Ahmed, prof. of Histology, Faculty of Medicine, Ain Shams University for her abounding patience, prolific assistance and help all through the beginning and end of this work. Without her sound advice, it would have been difficult to carry out the present work in a satisfactory way.

My deepest thanks and gratitude to Prof. Dr. Sami H. Hamed, Prof. of Histology, Faculty of Medicine, Ain Shams University for his consistent supervision, enthusiastic encouragement and everlasting help.

I am obliged to the kindness of Prof. Dr. Elham M. Gamal, Prof. of Histology, Faculty of Medicine, Ain Shams University for her skillful scientific guidance and valuable advice. She helped me through the beginning and final stages of this work. To her I am greatly indebted.

I would like to express my sincere appreciation and gratitude to Prof. Dr. Ezz El Din H. Helaiel, Prof. of Anatomy, Faculty of

Central Library - Ain Shams University

Medicine, Ain Shams University. His active support, supervision and endless help were of great value as regards the electron microscopy work.

My deepest thanks to Prof. Dr. Essmat Z. Geith, Head of Histology Department, Faculty of Medicine, Ain Shams University, for giving me the full facilities for a proper research work.

I am also indebted to all my professors and colleagues in Histology Department who were of continuous support and help.

Finally, I want to thank my Parents for their encouragement and help.

I have a special debt to my husband Eng. Mohamed Reda who supported me with much patience.

Central Library - Ain Shams University

# Contents

**Page**


1-**Introduction and aim of the work**. ..... 1

2-**Review of Literature** ..... 3

- *Histological events of the small intestine during the first 7 weeks of life* ..... 3
- *Small intestinal enzymatic pattern during the first 7 weeks of life.* ..... 11
- *Cell kinetics and proliferation of the small intestine during the first 7 weeks of life.* ..... 20
- *Pharmacokinetics of methotrexate.* ..... 25
- *The effects of methotrexate on the small intestinal mucosa*..... 27
- *Protective role of vitamin A.* ..... 37

3-**Material and Methods**..... 39

4-**Results** ..... 50

- *GI ( Preweaning age group )*..... 52
- *GII (Postweaning age group) + Recovery groups*..... 111
- *GIII (Young immature age group )*..... 215
- *Electron microscopic results*..... 291

5-**Discussion**..... 343

6-**Summary and Conclusion**. .....362

7-**Abstract**.....367

8-**References**. ..... 369

9-**Arabic summary**. .....


Central Library - Ain Shams University

Central Library - Ain Shams University

# *Introduction and Aim of the Work*

Central Library - Ain Shams University

Central Library - Ain Shams University

# INTRODUCTION AND AIM OF THE WORK

Children of acute lymphoblastic leukemia (ALL) and cancer patients undergoing methotrexate therapy, experience a variety of side effects. These are specially confined to changes in the gastrointestinal tract structures, as ulcerative stomatitis and diarrhea are frequent side effects and require interruption of the therapeutic regimen. Even haemorrhagic enteritis and death from intestinal perforation may occur ***(Gilman, Goodman, Rall and Murad, 1985).***

***Funk and Baker (1991)*** described the effect of the drug on the gut of rats at 24 and 48 hours after intraperitoneal injection of 2 mg/ kg body weight. It was characterized by stoppage of mitosis in the crypts, shortened villi and depressed activity of intestinal enzymes.

In view of enzymatic activity, ***Ramadan, Yousif and Ali (1992)*** reported an increase in the activity of the non specific esterases which could be due to the role of these enzymes to control the toxic effects of methotrexate.

***Nagai, Horie and Awazu (1993)*** recorded that co-administration of Vitamin A with methotrexate had a protective effect on the small intestinal mucosa.

Most of the studies concentrated on the effect of the drug on the mucosa of adult rats, inspite of the wide use of methotrexate in the management of acute

Central Library - Ain Shams University

lymphoblastic leukemia in children. Hence, it was important to study the changes in the mucosa of young immature rats during drug therapy.

**The aim of the present study** is to evaluate the effect of methotrexate on small intestinal mucosa in young immature rats below the age of 2 months, during the critical periods of small intestinal growth (breast feeding and food dependency), also to predict the protective role of vitamin A coadministration.

Central Library - Ain Shams University