

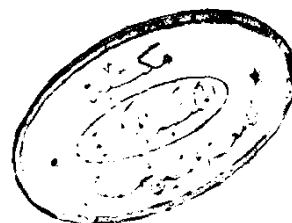
# **LEVAMISOLE THERAPY IN RHEUMATOID ARTHRITIS**

## **T H E S I S**

**Submitted in Partial Fulfilment of the  
Master Degree  
In  
( General Medicine )**

**By**

**Osman Adhame Foad Adhame**



**Supervisors**

**Prof. Dr.**

**FATHY TAMARA**

**Professor of Medicine**

**Prof. Dr.**

**MOHAMMED A. SALLAM**

**Professor of Medicine**

**Dr.**

**MOHAMMED R. BADDAR**

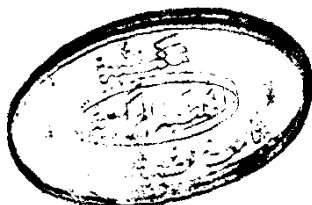
**A. Professor of Medicine**

**Dr.**

**ABDEL-GHANY SHAWKAT**

**Lecturer of Medicine**

**Faculty of Medicine  
Ain Shams University**



**1983**



قالوا سبحانك لا علم لنا إلا ما علمتنا  
إنك أنت العزيز الحكيم

— في صفة الله العظيم —



### A C K N O W L E D G M E N T

I would like to express my deepest gratitude and appreciation to my Professors Dr. MOHAMMED A. SALLAM and Dr. FATHY TAMARA, Professors of Medicine, Faculty of Medicine, Ain-Shams University.

It was through their enthusiastic Cooperation, unfailing help and constant advices that this work could come to existence.

I am greatly indebted to Dr. MOHAMMED R. BADDAR, Assistant Prof. of Medicine, Faculty of Medicine, Ain-Shams University and Dr. ABD EL GHANY S., Lecturer of Medicine, Faculty of Medicine, Ain Shams University, for their efficient supervision, meticulous revision of every possible details, kind encouragement and cooperation.

OSMAN A. FOUAD

## C O N T E N T S

\*\*\*\*\*

|                                                                      | Page |
|----------------------------------------------------------------------|------|
| ****                                                                 |      |
| * INTRODUCTION & AIM OF THE WORK -----                               | 1    |
| * REVIEW OF LITERATURE :                                             |      |
| - Rheumatoid Arthritis -----                                         | 2    |
| - Immunologic Abnormalities in<br>Rheumatoid Arthritis -----         | 29   |
| - Role of HLA System in Rheumatoid<br>Arthritis -----                | 32   |
| - Therapy in Rheumatoid Arthritis-                                   | 34   |
| ° Aspirin -----                                                      | 35   |
| ° Gold -----                                                         | 42   |
| ° D-penicillamine -----                                              | 48   |
| ° Corticosteroids -----                                              | 55   |
| ° Immunoregulatory drugs ---                                         | 58   |
| . Immunosuppressants e.g.<br>Methotrexate -----                      | 58   |
| . Immunostimulation and<br>immunostimulants e.g.<br>Levamisole ----- | 62   |

|                                                                                    |    |
|------------------------------------------------------------------------------------|----|
| ◦ History -----                                                                    | 63 |
| ◦ Chemistry -----                                                                  | 63 |
| ◦ Pharmacology -----                                                               | 65 |
| ◦ Mechanism of action -----                                                        | 67 |
| ◦ Immunologic properties --                                                        | 69 |
| ◦ Toxicology -----                                                                 | 72 |
| ◦ Drug interaction -----                                                           | 73 |
| ◦ Clinical application in<br>man -----                                             | 74 |
| . In normal subjects --                                                            | 78 |
| . In rheumatoid arthritis                                                          | 78 |
| - short term evaluation                                                            | 79 |
| - long term evaluation                                                             | 84 |
| ◦ Factors affecting responsive-<br>ness -----                                      | 86 |
| ◦ Adverse reactions of leva-<br>misole -----                                       | 88 |
| ◦ Comparison with other second<br>line drugs e.g Gold and<br>D-penicillamine ----- | 96 |
| ◦ How to use the drug -----                                                        | 97 |

|                              |     |
|------------------------------|-----|
| ⌘ MATERIAL AND METHODS ----- | 102 |
| ⌘ RESULTS -----              | 104 |
| ⌘ DISCUSSION -----           | 109 |
| ⌘ SUMMARY -----              | 115 |
| ⌘ REFERENCES -----           | 116 |
| ⌘ ARABIC SUMMARY -----       | 130 |

## I N T R O D U C T I O N

### INTRODUCTION AND AIM OF WORK

Levamisole, a potent anthelmintic drug against most nematodes, has recently been used as an immunostimulatory agent, and in several controlled studies, its therapeutic effect has been established in patients with rheumatoid arthritis.

Aim of this work is to evaluate the effect of levamisole in the Egyptian rheumatoid arthritis patients .

## REVIEW OF THE LITERATURE

## RHEUMATOID ARTHRITIS

### Definition (Mason, 1979)

Rheumatoid arthritis is a symmetrical peripheral polyarthritis characterised by inflammation of the synovium which leads to destructive joint change.

Although arthritis is the most prominent manifestation many other systems may be involved so that it can be more correctly called rheumatoid disease.

### Epidemiology : (Mason, 1979)

In general females are affected three times as commonly as males. The peak age of onset is between 35 and 50 years; but no age is exempt and ranges from childhood to the age of over 75 years.

### Aetiology (Mason, 1979)

#### . Infection :

The role of infection as an aetiological factor is still undetermined. A number of claims have been made that mycoplasmata and diphtheroids have been identified within rheumatoid synovial cells, but their role in the aetiology of rheumatoid arthritis remains unproven.

. Genetic :

Familial aggregations of the disease have been observed. This is associated with more severe disease (sero-positive and erosive), and the prevalence in the first degree relatives of such patients being three or five times greater than in normal controls.

Pathology : (Sokoloff, 1979)

Synovitis occurs in joints, tendon sheaths, and bursa. No pathognomonic features are found but the presence of lymphocytes and plasma cells occurring in clumps is characteristic. In the joint the proliferating synovium erodes the cartilage of joint margin invading the subchondral bone, producing the characteristic erosive change, visible radiologically. Once the bone cortex is breached the pumping action of synovial fluid when the joint is used may enlarge this to produce a cystic appearance. The proliferating synovium also spreads over the surface of the cartilage forming a pannus.

In the advanced stages absorption of bone ends may take place, and in weight-bearing joints trabecular collapse may occur. Such changes with involvement of periarticular soft tissues lead to subluxation, instability and

deformity. Ankylosis occasionally occurs.

Subcutaneous nodules occur in 25% of patients with rheumatoid arthritis, being found only in those with positive tests for rheumatoid serum factor. They commonly appear in pressure areas—over the olecranon, sometimes within the bursa at this site, and on the extensor aspect of the forearm. Similarly they may be found over the sacrum or ischial tuberosities. Not infrequently they occur in association with tendon sheaths, particularly in the hand, especially in relation to the flexor tendons in the palms. They are also found in relation to the Achilles tendon. Such nodules are characterised by the presence of a central area of fibrinoid necrosis, surrounded by a palisade of epithelioid cells.

Lymphocytes and plasma cells are prominent in the outer layers. Arteritis is an important feature and accounts for many of the systemic features of R.A. This may involve the smallest vessels where intimal hyperplasia results in local ischaemia.

In the larger vessels necrotic changes in the arterial wall resemble those seen in polyarteritis nodosa.

### CLINICAL PICTURE

The clinical manifestations of rheumatoid disease are highly variable. But its fully developed picture is easily recognized. (Mason, 1979).

The onset of articular signs of inflammation is usually insidious with prodromal symptoms of malaise, weight loss, vasomotor disturbances (e.g paraesthesia, Raynauds disease), and vague periarticular pain or stiffness. (Moberg & Edeland, 1973).

Less often the onset is acute, apparently triggered by a stressfull situation such as infection, surgery, trauma, emotional strain or the postpartum period.

The out-standing symptom of rheumatoid arthritis is pain which is often severe, although it may be of any degree of intensity. The pain is particularly severe when the disease is acute and the capsule is not yet chronically stretched.

This pain is typically aggravated by the use of the affected joint and weight-bearing stress, and relieved by rest. (Dorwart & Schumacher, 1974).

In any case, there is characteristically symmetrical joint swelling with associated stiffness, warmth, tenderness,

and pain.

This joint affection is progressive symmetrical peripheral polyarthrititis.

The pattern of joint involvement is one that includes the proximal interphalangeal and metacarpophalangeal joints of the hands, the wrists, and the lateral four metatarsophalangeal joints of the feet.

New joint involvement develops irregularly to include the larger limb joints, ankles, knees, elbows, and shoulders and often later the hips. The temporomandibular joints may be affected, usually transiently.

The spinal joints are usually spared with the important exception of the cervical spine where involvement of the atlanto axial joint, and of the facet joints of the upper cervical spine is characteristic (in contrast to degenerative joint disease which affects the lower cervical spine). (Dorwart & Schumacher, 1974).

Involvement of the crico-arytenoid joint and those of the middle ear has been described.

The predominant sign of rheumatoid arthritis is joint swelling, and it is impossible to diagnose this disease