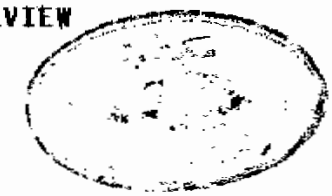
HORMONE RESPONSIVE TUMOURS OF THE FEMALE GENITAL TRACT: A CLINICO-PATHOLOGICAL REVIEW



THESIS

Submitted for Partial Fulfilment of

M. Sc. Pathology

Subsidiary Obstetrics and Gynaecology

By:

MONA KHALED EL SHISHINI

M.B., B.Ch.

Supervised by:

Dr. MOHAMED EL-SHAWARBY
Assistant Professor of Pathology
Faculty of Medicine
Ain Shams University

Dr. SANAA SAMMOUR
Lecturer of Pathology
Faculty of Medicine
Ain Shams University

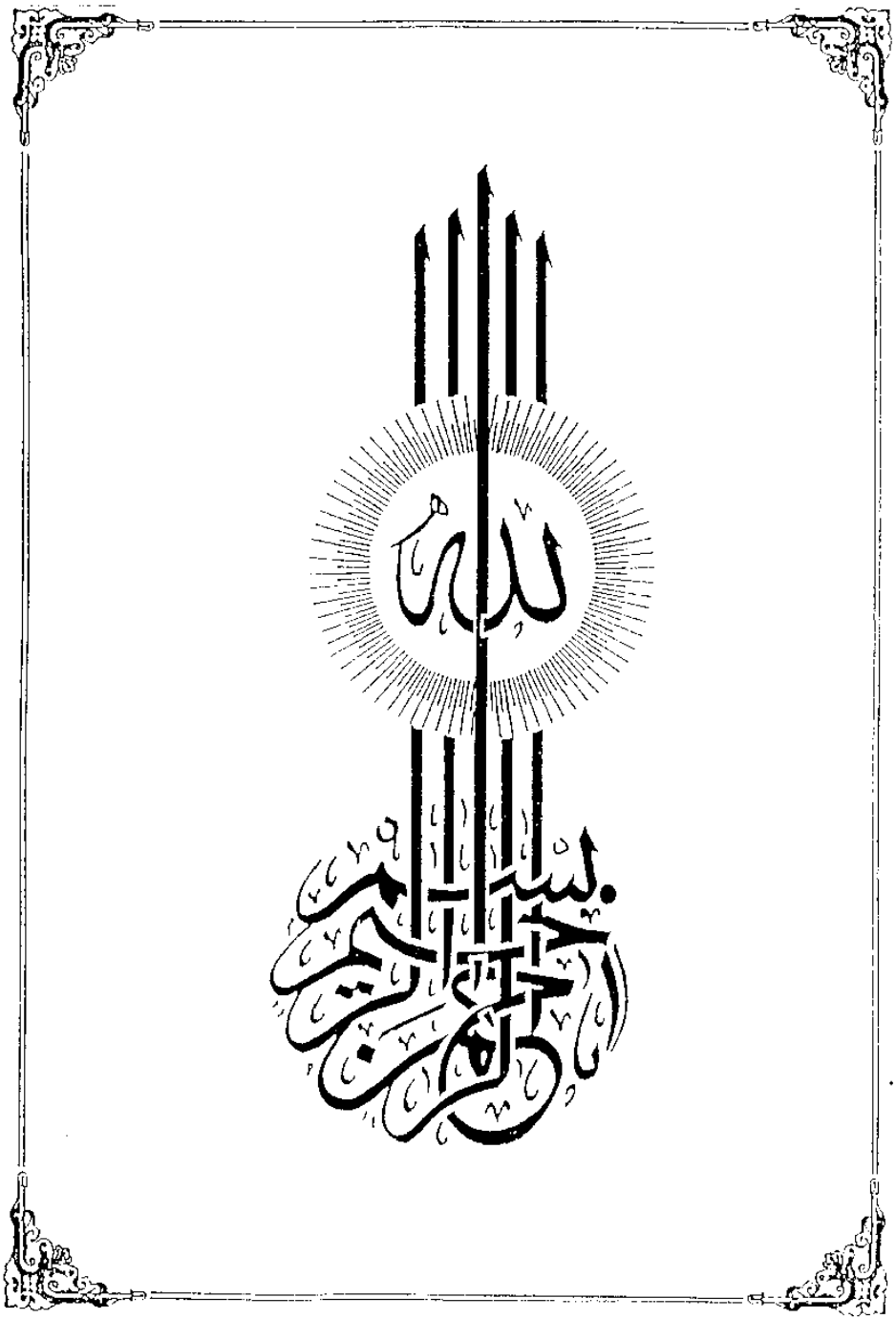
Cairo
1986

ACKNOWLEDGEMENTS

I would like to take this opportunity of giving my deep and sincere thanks to **Dr. Mohamed El-Shawarbi**, Assistant Professor of Pathology at Ain Shams University, for his invaluable advice and assistance to me during the course of this study.

I would also like to express my thanks and appreciation to **Dr. Sanaa Sammour**, Lecturer of Pathology at Ain Shams University for her great help to me in the completion of this work.

I would further like to express my gratitude to **Professor Sammour** and my colleagues in the Cytodiagnostic Unit for their encouragement.



CONTENTS

	Page
- INTRODUCTION	1
- AIM OF THE WORK	3
- REVIEW OF THE LITERATURE	4
- Mechanism of action of steroid hormones	4
- Different techniques of detection	17
- Uterus	20
- Myometrium	20
- Endometrium	23
- Normal endometrium	23
- Hyperplastic endometrium	26
- Endometrial tumours	27
- Cervix	37
- Fallopian tubes, vulva and vagina	41
- Ovary	42
- SUMMARY	56
- REFERENCES	
- ARABIC SUMMARY	

Introduction

INTRODUCTION

The steroid hormones have molecular weights of about 300 . They can readily diffuse into all cells of the body, but as we know, they trigger characteristic reactions only in cells of their target tissues. The high affinity of these target tissues for a steroid comes from the capacity of their cells to produce special cytoplasmic proteins, which specifically and rapidly intercept and bind the hormone as it diffuses into the cell. Because of that "welcoming function", the cytoplasmic protein has been named a "receptor" (Dallenbach, 1981, De Sombre, et al., 1984).

Muldoon (1980) and Grady, et al., (1982) stated that the specificity of the reaction of tissues to steroid hormones is due to the presence of intracellular receptor proteins.

It is the affinity and specificity of the receptors together with the large concentration of receptors in cells which allow a small amount of hormone to produce a biologic response (Speroff, et al., 1983).

Most cells of a target organ maintain about 10,000 steroid receptors in their cytoplasm (Dallenbach, 1981). Gorski and Gannon, (1976) estimate about 16,000 receptors per cell. The number may fluctuate however, depending on the intensity and duration of prior hormonal stimulation, on the degree of cellular differentiation and on such factors as phase of cell cycle, cell age, metabolism, and genetic state (Gehring, et al., 1971, Kirkpatrick, et al., 1971, Sibely and Tomkins, 1974), nutrition, pharmacologic pretreatment, effects of other hormones, pathologic states and so on (Dallenbach, 1981).

To be able to respond to a steroid hormone a target cell must produce receptors specific for that hormone. Consequently receptor proteins specific for oestrogens or progesterone or androgens have been identified (Dallenbach, 1981).

AIM OF THE WORK

The aim of the present work is to review the literature regarding the receptors of gynaecologic cancers with special emphasis on the chemical and histopathological importance.

Review Of The Literature

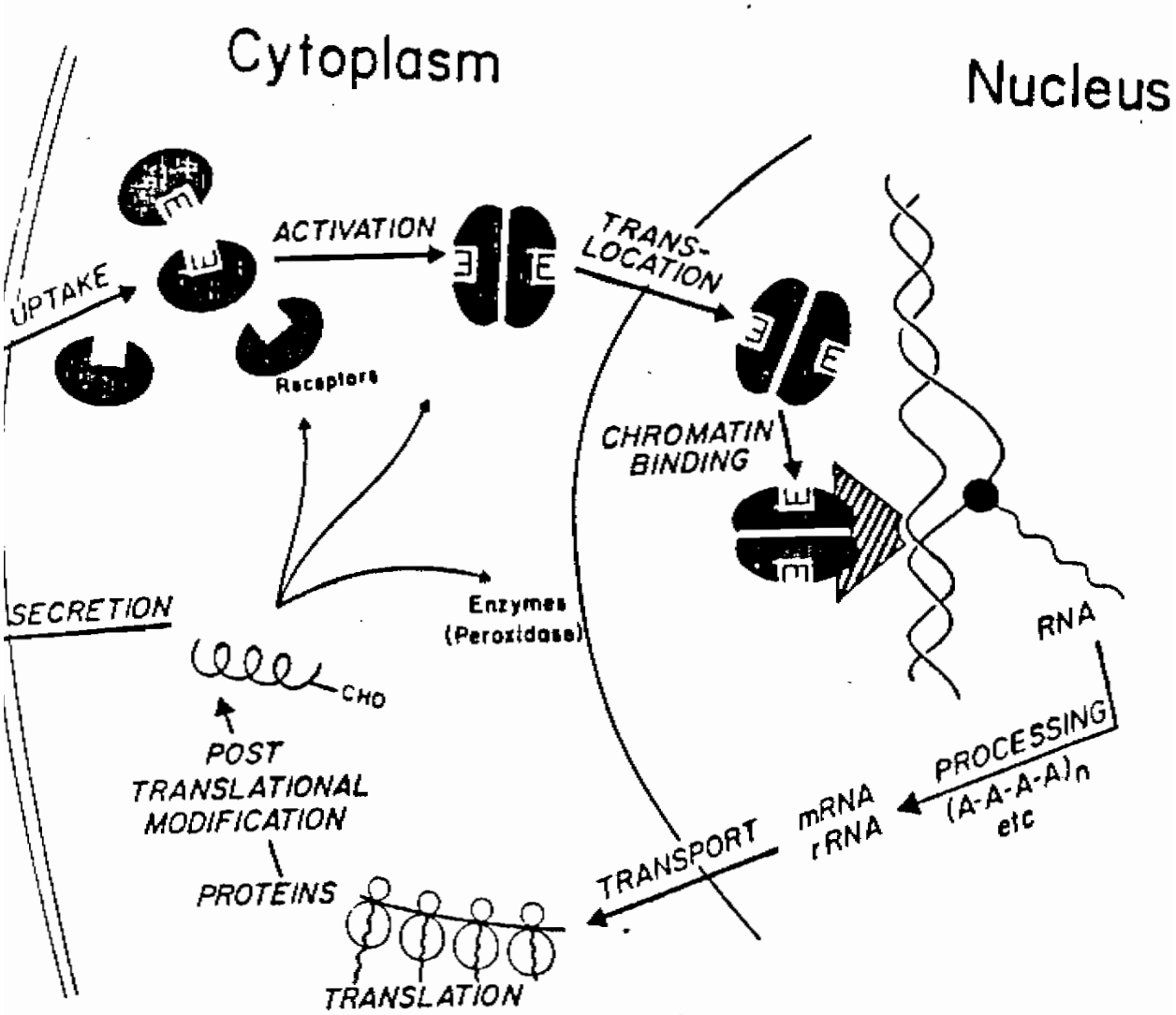
Mechanism of Action of Sterold Hormones

Speroff, et al., (1983) summarized the mechanism of actlon of sterold hormones by the following steps which include:

1. Diffusion across the cell membrane;
2. Binding to cytoplasmic receptor protein and transfer of the hormone receptor complex across the nuclear membrane to the nucleus;
3. Translocation and transformatlon;
4. Binding of a hormone receptor complex to nuclear DNA;
5. Synthesis of messenger RNA (mRNA);
6. Transport of mRNA to the ribosomes, and finally, protein synthesis in the cytoplasm whlch results in specific cellular actlvlty (Fig. 1).

Baxter and Funder (1979), Dallenbach, (1981), and Speroff, et al., (1983) stated that the receptors actually have two functions. The first is to recognise and select out the different types of hormones in the fluid bathing the cell, the appropriate hormone acting as a signal. The second is to relay that signal to the nucleus where it specifically effects the genome bringing about definite changes in the cell. All sterold hormones act alike.

FIGURE (1) : Schematic diagram of the oestrogen interaction pathway and biochemical response in target cells.



1. Diffusion across the cell membrane

Speroff, et al., (1983) and De Sombre, et al., (1984) mentioned that steroid hormones are rapidly transported across the cell membrane by simple diffusion.

Initial studies in vivo (Glascock and Hoekstra, 1959, Jensen and Jacobson, 1960) demonstrated that target tissues for the hormone could take up and retain physiologic amounts of radiolabelled oestrogens against a concentration gradient with the blood and that this uptake occurred without requiring metabolism of the active oestrogen (De Sombre, et al., 1984).

2. Binding to cytoplasmic receptor protein and transformation hormone receptor complex

The steroid entering the cell rapidly binds to its receptor protein, believed to be present in excess amounts as free receptor in the extranuclear region of the cell (Speroff, et al., 1981, De Sombre, et al., 1984).

Speroff, et al., (1981) named hormones which bind to receptors as "ligands" which are defined as molecules that bind to receptors and produce spe-

cific biologic responses.

In the cytoplasm oestrogen receptors (ER) exist in 4S forms and 8S forms. The larger 8S is probably a storage form, while the 4S is the traditional active receptor (Speroff, et al., 1983, De Sombre, et al., 1984).

3. Translocation and transformation

The physiologic response to steroid hormones requires movement of the hormone and receptor into the nucleus to interact with DNA. This movement is known as "translocation" (Speroff, et al., 1983).

Dallenbach (1981) stated that the process of translocation from cytoplasm to nucleus proceeds quickly but apparently requires no energy.

It is not exactly known how the hormone receptor complex enters the nucleus. Speroff (1983) and Dallenbach (1981) postulated that the shape of the receptor (an elongated ellipsoid) and its molecular weight (referred to as "conformational change") are important in the process, whereby it becomes activated, enabling it to slip through nuclear pores, and to enter the

nucleus where it signals specific changes revealing or producing a nuclear binding site. This latter process is called "transformation", a change from an inactive to an active complex.

With ER, transformation is associated with a change in the sedimentation rate on sucrose gradient from 4S to 5S smaller and larger molecules respectively (Speroff, et al., 1983, De Sombre, et al., 1984).

4. Binding of a hormone receptor complex to nuclear DNA

On arrival in the nucleus the hormone-receptor complex interacts and binds with high affinity to so-called "acceptor" sites on the chromatin, inducing thereby changes in numerous gene loci (Gorski and Gannon, 1976, Yamamoto and Alberts, 1976, Baulieu, 1979, Baulieu, et al., 1980, Dallenbach, 1981, and De Sombre, et al., 1984).

For the ER complex, there seems to be more acceptor sites than receptors, thus the nuclear binding sites never become saturated (Dallenbach, 1981).

Dallenbach's (1981) statement that the acceptor sites for the progesterone receptor (PR) complex also outnumber the PR seems probable. Speroff, et al., (1983) found that the PR is 7S in size and is transformed to a smaller 5.5S form with nuclear relocation.

Studies with progesterone explained how they believe the dimeric progesterone receptor (PR) (subunits A and B) bind at different but specific acceptor sites on chromatin to activate genes (Dallenbach, 1981).

When the PR complex enters the nucleus the B subunits bind to a specific acceptor protein on the chromatin, where a special ATP (adenosine triphosphate) fraction of the non-histone chromosomal proteins is located. The other subunits A, are unable to bind to intact chromatin, and dissociate from the B subunits and react with specific genes situated nearly on the chain of naked DNA. The choice of specific genes is presumably determined by B subunits as they bind with the ATP fraction or some protein of it. The reaction of the subunits A with the specific genes attracts a molecule of RNA polymerase to