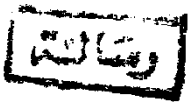
IMMUNOLOGICAL MECHANISMS IN MALIGNANT TUMOURS



THESIS

Submitted in partial fulfilment of
M. Sc.Degree
(PATHOLOGY)

BY

THANAA EL-SAYED AHMED HELAL

Supervised By:
Prof. Dr. Mourad Ali Sherif,
Head of Pathology Department, Faculty of Medicine
Ain Shams University.

Dr. Mohammed El-Shawarbi,
Lecturer of Pathology, Faculty of Medicine,
Ain Shams University.

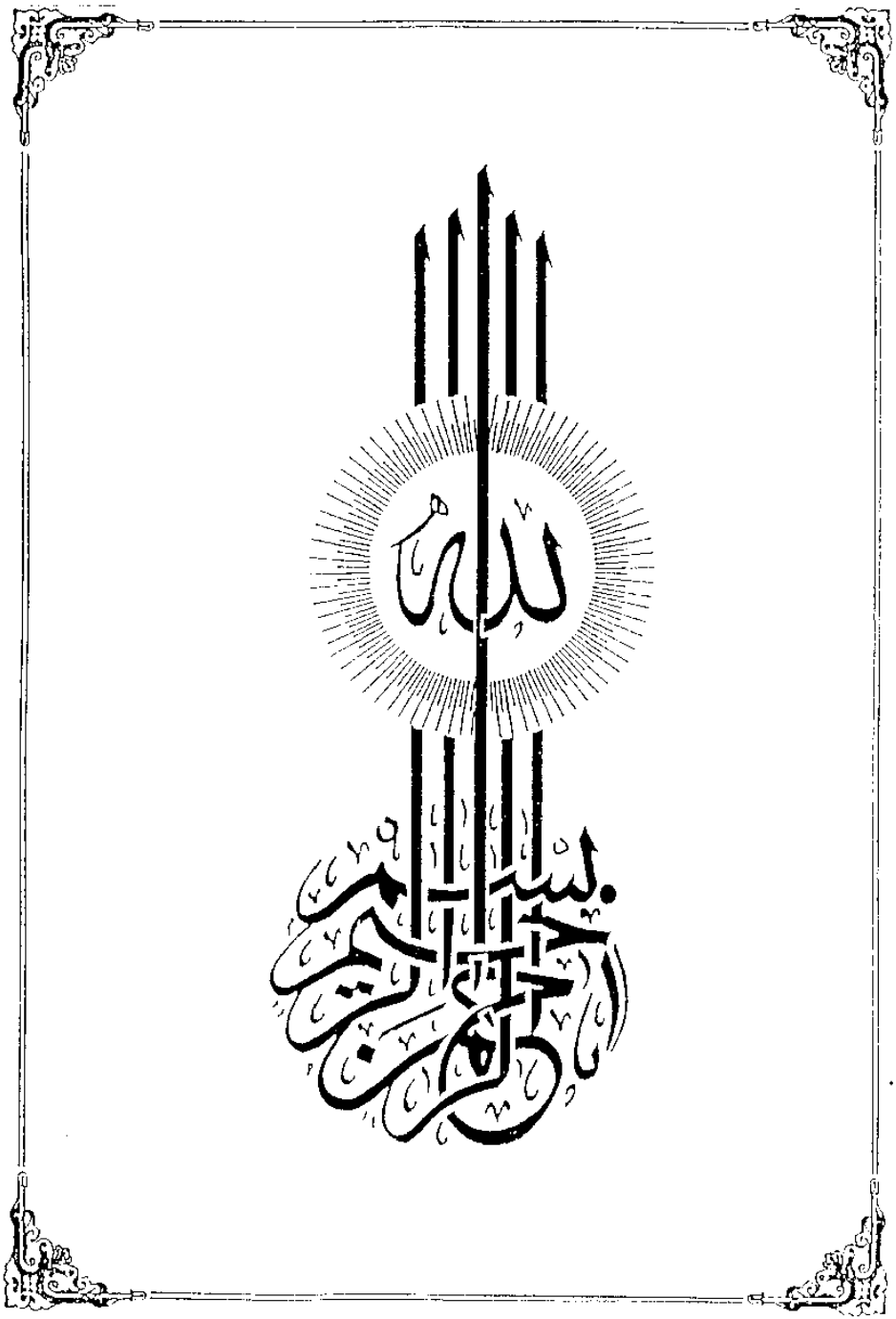
AIN SHAMS UNIVERSITY
FACULTY OF MEDICINE

1981

ACKNOWLEDGEMENT

This Thesis has been completed under the kind supervision of Prof. Dr. Mourad Ali Sherif , Head of Pathology Department. I am much indebed to him, for his fathery attitude and kindness towards me.

I am deeply indebted to Dr. Mohammed El-Shawarbi, Lecturer of Pathology, who has spared no effort to advise me and guide me throughout every step of this study.



C O N T E N T S

- - -

AIM OF THE WORK

It is more or less accepted today that most human tumours can elicit an immune response in the tumour - bearing host. The role of immunologic mechanisms, both cellular and humoral, in tumour growth has been extensively investigated. It is generally agreed upon that cell-mediated immunity has a "killing" effect tending to reject the tumour growth. The role of humoral immunologic mechanisms however, is still a matter of dispute. It has been suggested that humoral antibodies act as blocking factors, counteracting the killing effect of cellular immunologic mechanisms, thereby facilitating growth and spread of the tumour (enhancement). However, there is some evidence that blocking factors may be antigen - antibody complexes or free antigen (liberated from the tumour), rather than antibody. Whatever the nature of the blocking factors, they are considered as an escape mechanism by which the tumour can escape the killing effect of cellular immunity. In addition to this escape mechanism, other mechanisms have been proposed.

The aim of this work was to correlate the clinical stage of breast cancer, presence or absence of lymphocytic infiltrate in the tumour and reaction in draining lymphnodes with serum immunoglobulin levels and presence or absence of antibodies reactive with tumour in

serum, in an attempt to study the role of humoral immunity in the outcome of breast cancer.

To acheive this, we studied sixteen cases of breast cancer which is considered the commonest cancer in Egyptian females, so it has been taken as an example of malignant tumours. These cases were examined clinically for the stage, histologically (the tumour and its draining lymphnodes) and immunologically (direct immunofluorescence, indirect immunofluorescence and quantitation of serum immunoglobulins).

The resultsof our study are discussed utilizing the available literature on tumour immunity, which is also reviewed.

ANATOMY OF THE FEMALE BREAST*

The mammary gland consists of glandular tissue, fibrous tissue connecting its lobes, and adipose tissue in between the lobes. The subcutaneous tissue encloses the gland (but does not form a distinct capsule) and sends numerous septa into it to support the lobules. Fibrous processes are passing forwards to the skin papillae forming the suspensory ligament of Cooper. The normal gland consists of 15 - 20 lobes, each lobe is composed of multitude of lobules. These lobules are connected together by areolar tissue, blood vessels and ducts. Each lobe is drained by one duct "lactiferous duct". The lactiferous duct is dilated beneath the areola to form the "lactiferous sinus".

The Blood Supply of The Breast:

The arteries are derived from thoracic branch of the axillary artery, internal thoracic artery and intercostal arteries. The veins form anastomotic circle around the base of the nipple called "circulus venosus". From this circle and from the glandular tissue, branches drain the blood to the circumference of the breast. These branches are ending in the axillary and internal thoracic veins.

---

* Last, R.J. (1972): Anatomy, Regional and Applied". 5thed. Churchill Livingstone. Edinburgh and London, Page 101.

Nerves of The Breast:

Nerves are derived from anterior and lateral cutaneous branches of the 4th, 5th and 6th thoracic nerves. These nerves convey the sympathetic fibres to the breast.

EMBRYOLOGY OF THE BREAST*

The human breast makes its first appearance in the sixth week of embryonic development as an ectodermal thickening extending from the axilla to the groin, a distinct linear deviation called "mammary ridge" or milk line. Lens-shaped thickenings appear along the milk line, presagging the sites of developing breasts. In man the caudal two-thirds of the line disappear rapidly and the pectoral thickening progresses with the ultimate formation of a breast. In the fifth month of embryonic life, the human develops 15 to 20 solid cords which fan out beneath the skin in the underlying connective tissue. These primary milk ducts branch and the ends develop club-shaped dilatations. During this same period, the point in the skin corresponding to the nipple develops a small depression. At birth the breast is represented by a slight pit pierced by 15 - 20 openings into the primary milk ducts. The areola is a slight thickening in the skin which contains few glands (of Montogomery).

---

* Hamilton, W.J., Boyd J.D. and Mossman H.W. (1969): "Human Embryology". 3rd edition. W. Heffer and Sons LTD. Cambridge, England. P. 428.

HISTOLOGY OF THE BREAST*

The mammary glands are modified sweat glands. They are compound alveolar glands. They are not functioning except during lactation. Their structure undergoes cystic changes during the fertile period of women. In resting condition the nipple and areola are always deeply pigmented. They are usually brownish pink in color, containing large sweat and sebaceous glands, but not hairs. The glandular tissue is very little. The areolar and adipose tissues are large in amount. The lobules of resting mammary glands contain groups of alveolar ducts which lined with cuboidal epitjelium. Myo-epithelial cells are impored between the basement membrane and the bases of the epithelium. The main lactiferous ducts are lined by stratified squamous epithelium, within the nipple, the ducts are separated from one another by longitudinal and circular bundles of smooth muscle fibres.

---

* Ham A.W. (1974): "Histology", 7th edition. J.B. Lippincott Company. Philadelphia and Toronto. Page 890.

PHYSIOLOGY OF THE BREAST*

The physiological changes which occur in the breast are closely related to reproductive system. They include: growth and involution related to the age, the changes which are associated with menstrual cycle and the changes which are due to pregnancy and lactation.

Growth And Involution:

At birth, the breast consists of a branching system of ducts emptying into a well developed nipple. Few days after birth - in both sexes - there is a breast enlargement with slightly milky secretion from the nipple. After a week or so, the glands lapse into inactive state of childhood. In female around the age of 10 - 15 years, adolescent breast is developed. It grows and becomes protuberant, the areola enlarges and becomes pigmented. Well development occurs by the time of menstruation. The adult's breast characters (fullness, density and nodularity) depend chiefly upon two factors. The first factor is corpulence of the individual. Since the breast-in great parts - is made up of fat, obese women usually have a large and firm breast. Second factor is whether the breasts are functioning or not. In child-bearing

---

* Ganong W.F. (1977) "Review of Medical Phisiology" 8th edition. Lange Medical Publications. Endocrinology and Metabolism, Page 342.

period and breast feeding, breasts are softer and less nodular. In never functional breasts, increased nodularity and density are more characteristic. With completion of menopause the breasts commonly decrease in size and become less dense. There is frequently a decrease in the number and size of the gland field with increase in the elastic stroma.

Breast Changes Associated With Menstrual cycle:

Engorgement phenomenon is closely correlated with menstrual cycle. This has several components of increase in size, density, nodularity and sensitivity. Engorgement disappears with completion of menstruation. The increase in size may be obvious and is much regular phenomenon. The increased nodularity of the breast during menstrual period is commonly confused with fibroadenosis. The increased sensitivity of the breast is usually mild. It must be assumed that these changes are due to blood or lymph engorgement, or due to increase in the extracellular fluid tension.

Changes in The Breast Due to Pregnancy and Lactation:

The areolar skin glands become more prominent and areolar skin darkens , in early conception. The breast enlarges steadily during the last half of pregnancy. Clostrum is firstly secreted after delivery. Few days later, milk comes in. The breast approximately returns to

THE IMMUNE RESPONSE, HYPERSENSITIVITY REACTIONS AND REACTION TO HOMOGRAFTS:

Before dealing with the various aspects of cancer immunity, a brief account will be given on the immune response in the human body, hypersensitivity reactions and the reaction of the body to homografts. These subjects are closely related to our main topic and their review, although brief, will greatly help in the understanding of the immune response to cancer. This account is based on the knowledge reviewed by Anderson and Kissane (1977), Roitt (1977), Sherif and Ghaly (1979) and Walter and Israel (1979).

The Immune Response:

The immune response in the body is initiated when an antigen enters the body. Introduction of an antigen will result in either or both of the following reactions:

1. Synthesis and release of free antibody into blood and other body fluids (humoral antibody). This antibody acts for example by direct combination with and neutralization of bacterial toxins, by coating bacteria, enhancing their phagocytosis and so on.

2. Production of sensitized lymphocytes which release a number of soluble mediators known as lymphokines or cell-bound antibodies. These are the effectors of cell-mediated immunity expressed in such reactions as the rejection of skin transplants.

Humoral antibodies (immunoglobulins, Igs) are classified into the following groups:

- IgG is the most abundant immunoglobulin particularly in the extravascular fluids where it combats micro-organisms and toxins. It fixes complement, binds to phagocytic cells and crosses the placenta.

- IgA is present mainly in the seromucous secretions where it is the major immunoglobulin concerned in the defence of external body surfaces.

- IgM exists in plasma. It is a very effective bacterial agglutinator and mediator of complement-dependent cytolysis.

- IgD is present on the lymphocytes and functions as antigen receptor.

- IgE is probably of importance in certain parasitic infections and it is responsible for the symptoms of atopic allergy.

Cell-bound antibodies (lymphokines) include: Macrophage migration inhibition factor, macrophage activation factor, specific macrophage arming factor, mnonuclear chemotactic factor, skin reactive factor, lymphocyte mitogenic factor, cytostatic (lymphotoxin) factor and interferon.

The important effector cell in both types of immune response is the small lymphocyte. Primitive lymphoid cells from the bone marrow appear to be differentiated

into two small lymphocyte populations. The first are the "T lymphocytes" (thymus-dependent) which are responsible for cell-mediated immunity. The second are the "B lymphocytes" (Bursa-dependent) which are concerned with synthesis of humoral antibodies.