# Introduction

Sir James Paget first described Paget's disease of the breast in 1874. He reported a chronic eczematous disease on the skin of the nipple and the areola in 15 women, with an associated intraductal carcinoma of the underlying mammary gland. In 1881, Thin illustrated the first histological description of Paget's disease. Crocker described the first case of extra mammary paget's disease on the glans penis in 1889. In 1901, Dubreuilh reported a case on the vulva. Mammary Paget's disease occurs almost exclusively in women. Involvement of the male breast is rarely reported. A similar disease involving the skin of female and male external genitalia (i.e., vulva, glans penis) is known as extra mammary Paget's disease. Histological features of mammary Paget's disease and extra mammary Paget's disease are similar; however, the histogenesis and the pathogenesis are different ***(Kao, 2009)***.

Certain women seem to be at a higher risk of developing breast cancer. This includes nullipara women's, women which get pregnant late in life, early menarche or who had a late menopause, and women who have a strong family history of breast cancer ***(Eds Winchester et al.,2008)***

Scientists do not know exactly what causes Paget's disease of the nipple, but two major theories have been suggested for how it develops. One theory proposes that cancer cells, called Paget's cells, break off from a tumor inside the breast and move through the milk ducts to the surface of the nipple,. This theory is supported by the fact that more than 97 percent of patients with Paget's disease also have underlying invasive breast cancer or duct carcinoma in situ (DCIS). The other theory suggests that skin cells of the nipple spontaneously become Paget's cells. This theory is supported by the rare cases of Paget's disease in which there is no

underlying breast cancer, and the cases in which the underlying breast cancer is found to be a separate tumor from the Paget's disease ***(Harris et al., 2004)***.

The first symptom is usually a scaly, red rash affecting the nipple and sometimes the dark area of skin surrounding the nipple. The rash always affects the nipple first, and may then affect the areola. It does not go away and may become sore. The skin of the nipple and areola may be inflamed. There may also be crusting, bleeding and ulceration. Some women have an itching or burning sensation. Fluid may leak from the abnormal area of cells. The nipple may turn inwards. There may or may not be a lump in the breast. Around half of women who have Paget's disease have a breast lump that can be felt at the time it is diagnosed ***(Daniel, 2005)***.

The appearance of the breast may suggest the diagnosis to your doctor. Certain tests will be needed to help make the diagnosis definite, and to find out whether the cancer has spread. Biopsy This is the most important test to find out if cancer is present. A small sample of tissue is taken from the breast and then examined under a microscope to check for signs of cancer.

**Mammogram** may be used to look for changes in the affected breast, and to check the other breast.

**Ultrasound scan:** In this test sound waves are used to make up a picture of the breast tissue. The test is completely painless and takes 5-10 minutes ***(Eds Donegan and Spratt, 2002)***

Surgery is the most common treatment for Paget's disease of the nipple. The specific treatment often depends on the characteristics of the underlying breast cancer. A modified radical mastectomy may be recommended when invasive cancer or extensive DCIS has been diagnosed. In this operation, the surgeon removes the breast, the lining over the

chest muscles, and some of the lymph nodes under the arm. In cases where underlying breast cancer is not invasive, the surgeon may perform a simple mastectomy to remove only the breast and the lining over the chest muscles ***(DeVita, et al., 2004)***.

Alternatively, patients whose disease is confined to the nipple and the surrounding area may undergo breast-conserving surgery or lumpectomy followed by radiation therapy. During breast-conserving surgery, the surgeon removes the nipple, areola, and the entire portion of the breast believed to contain the cancer. In most cases, radiation therapy is also used to help prevent recurrence. Adjuvant treatment may be part of the treatment plan, depending on the type of cancer and whether cancer cells have spread to the lymph nodes. Radiation treatment is a common adjuvant therapy for Paget's disease of the nipple following breast-conserving surgery. Adjuvant treatment with anticancer drugs or hormone therapies may also be recommended, depending on the extent of the disease and prognostic factors ***(DeVita, et al., 2004).***

Paget's disease of the breast is associated with a poor prognosis, which is worse if the lesion is associated with an underlying palpable mass. ***(Piekarski et al., 2004)***.

# Aim of the Work

The present study was designed to standardize clinicopathological criteria for paget's disease of the breast and its principal of management.

# Anatomy of the Breast

## Embryological Origin

The epithelial lining of the ducts and acini of the breast is developed from ectoderm and the supporting tissue is derived from the mesenchyme. On each side of the ventral surface of young embryo, a thickened band of ectoderm develops (the milk ridge).1t extends from the axilla to the inguinal region. In the human, the whole of this ridge atrophies, except only a small portion in each pectoral region from which the breast arises. Accessory breast tissue will form along the course of the milk ridge, if it does not disappear outside the area where the breast normally develops.

Normally, a tiny portion of the ridge which is going to form the breast enlarges projecting slightly on the skin and extending deeply in the shape of buds which form long slender tubes from which the ducts and secreting tissue of the breast are formed. The nipple is either flat or depressed at birth, but later it projects beyond the surrounding skin **(*Ellis et al.,1993).***

***Breast development and embryology:***

Appreciation of the stages of breast development facilitates the understanding of many benign and malignant states that come to clinical attention. During adolescence, the breast is composed primarily of dense fibrous stroma and scattered ducts lined with epithelium. Puberty is measured by age of breast development and onset of pubic hair begins between ages 9 and 12, and menarche begins about 12 to 13 years of age. These events are initiated by low amplitude nocturnal pulses of gonadotropins, which raise serum estradiol concentration. In the breast, this hormone-dependent maturation (the larche) entails increased deposition of fat, formation of new ducts by branching and elongation, and the

first appearance of lobular units. This process of growth entails cell division and is under the control of estrogen, progesterone, adrenal hormones, pituitary hormones, and trophic effects of insulin and thyroid hormones ***(Harold et al., 1993).***

There is evidence that local growth factor networks are also important, including epidermal growth factor, which can replace estrogen in breast development. The exact timing of these events and the coordinated development of both breast buds may vary from the average in individual patients. The term (prepubertal gynecomastia) refers to the symmetrical enlargement and projection of the breast bud in a young girl before the average age of 12 years, unaccompanied by the other changes of puberty ***(Beer, 2002).***

The postpubertal mature or resting breast contains fat, stroma, lactiferous ducts, and lobular units. During phases of the menstrual cycle or in response to exogenous hormones, the breast epithelium and lobular stroma undergo cyclic stimulation. It appears that the dominant process is hypertrophy and alteration of morphology rather than hyperplasia. In the late luteal (premenstrual) phase, there is an accumulation of fluid and intralobular edema. It is probable that this edema produces both pain and breast engorgement. On physical examination, and even by mammography, this fluid accumulation leads to increased nodularity and may be mistaken for a dominant tumor ***(Copleland et al.,1987)***.

Ill-defined masses in premenopausal women are correctly observed through the course of one or two menstrual cycles ***(Copleland et al.,1987)***.

Finally, any alteration in the periodicity of the menstrual cycle, such as anovulatory cycles, can cause accentuation of engorgement, pain, and nodularity. With pregnancy, there is diminution of the fibrous stroma to accommodate the hyperplasia of the lobular units. This formation of new acini or

lobules is termed the (adenosis of pregnancy) and is influenced by high circulation levels of estrogen, progesterone and by prolactin that steadily increase during gestation. After birth, there is a sudden loss of the placental hormones. A continued high level of prolactin is the principal trigger for lactation. The actual expulsion of milk is under hormonal control and is caused by the contraction of the myoepithelial cells that surround breast ducts and terminal ductules. There is no evidence for innervation of the myoepithelial cells; their contraction appears to be in response to the pituitary-derived peptide oxytocin. Stimulation of the nipple appears to be the physiologic signal for both the continued pituitary secretion of prolactin and for the acute release of oxytocin ***(Copleland et al.,1987).***

When breast-feeding ceases, there is a fall in prolactin and no stimulus for release of oxytocin. The breast then returns to arresting state and to the cyclic changes induced when menstruation begins again ***(Beer , 2002).***

With the approach of menopause, phases of the menstrual cycle may not be as symmetrical and regular. This irregularity can induce functional nodularity and breast pain in areas where there was none earlier years. Menopause is defined by a cessation in menstrual flow for one year. It usually occurs between ages 40 and 50 years. It may be accompanied by constitutional symptoms such as diaphoresis, vaginal dryness, urinary tract infections, and cognitive impairment. For the breast, menopause results in involution and general decrease in the epithelial elements of the resting breast. These changes include increased fat deposition, diminished connective tissue, and the disappearance of lobular units ***(Chummy , 2006).***

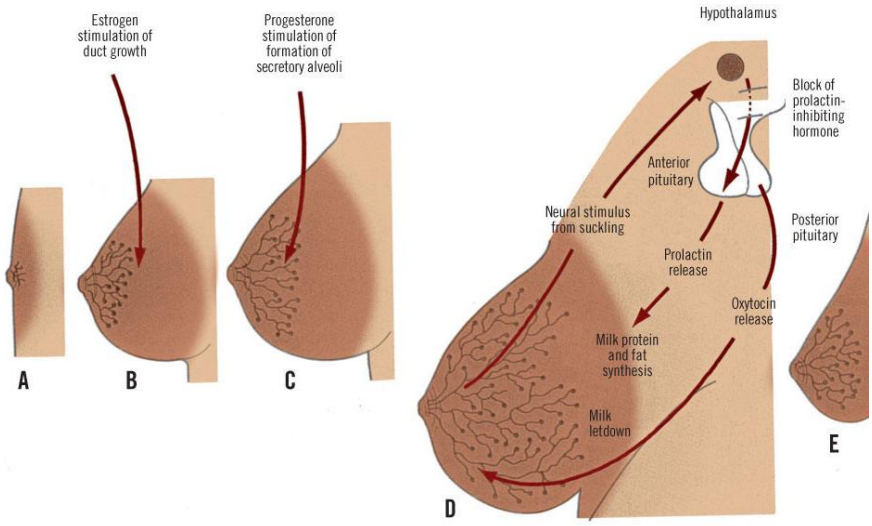


**Fig. (1)**: Development of mammary ducts and hormonal control of mammary gland development and function.
A. Newborn. B. Young adult. C. Adult. D. Lactating adult.
E. Post lactation ***(Skandalakis et al., 2006).***

## *Anatomical features of the breast*

Each breast (right or left) is a rounded elevation present on the front of the upper part of the thorax, over the pectoral region. Over the centre of the breast the skin shows a dark circular area which is called the areola. In the centre of the areola there is a conical projection called the nipple ***(Singh, 2002).***

The adult female breast is located within the superficial fascia of the anterior chest wall. The base of the breast extends from the second rib above to the sixth or seventh rib below, and from the sternal border medially to the midaxillary line laterally. Two-thirds of the base of the breast lies anterior to the pectoralis major muscle; the remainder lies anterior to the serratus anterior muscle (Fig. 1). A small part may lie over the aponeurosis of the external oblique muscle ***(Skandalakis et al., 2006).***

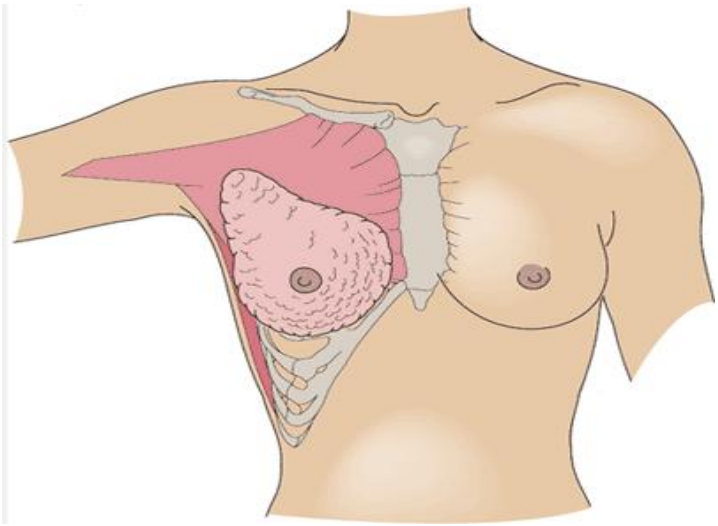

**Fig.(2):** The adult female breast. The upper and medial portions of the breast rest on the pectoralis major muscle, and the inferolateral portion rests on the serratus anterior ***(Morrow and Khan, 2006).***

From the upper lateral part of the gland an extension of glandular tissue passes through an aperture in the deep fascia over the axilla to enter the latter (The aperture is the foramen of Langer). This extension is called the axillary tail ***(Singh, 2002).***

The lobule is the basic structural unit of the mammary gland. The number and size of the lobule vary enormously; they are most numerous in young women. From ten to over 100 lobules empty via ductules into a lactiferous duct, of which there are 15-20 each lactiferous duct is lined with a spiral arrangement of contractile myoepithelial cells and is provided with a terminal ampulla, a reservoir for milk or abnormal discharges ***(Sainsbury, 2004).***

The ligaments of Cooper are hollow conical projections of fibrous tissue filled with breast tissue, the apices of the cones being attached firmly to the superficial fascia and thereby to the skin overlying the breast. These ligaments

account for the dimpling of the skin overlying a carcinoma ***(Sainsbury, 2004).***

**Blood supply of the breast:**

**Arterial supply:**

***Blood supply to the breast is from multiple sources:***

1- ***The internal mammary artery:*** This arises from first part of subclavian artery, gives perforating branches (most notably the second to fifth perforators) supply the breast.

2- ***The thoracoacromial artery:*** it is a short branch of second part of the axillary artery.

3- ***The lateral thoracic artery:*** from second part of axillary artery.

4- The terminal branches of the third to eighth intercostal vessels and the vessels to serratus anterior.

The internal mammary vessels accounts for 60% of the total breast blood supply. The lateral thoracic supply contributes about 30% of total breast vascularity ***(Skandalakis et al.,2006).***

The medial breast portion receives from the branches of the internal thoracic artery, especially in the 2nd and 3rd intercostal spaces. The lateral part is supplied by the lateral thoracic artery. Inferiorly, it is supplied by the anterior intercostal arteries, especially in the 4th and 5th intercostal spaces. The superior portion receives perforators of the supra-clavicular and the thoracoacromial arteries. These vessels anastomose below the NAC, and then follow the connective tissue framework to penetrate the gland ***(Corduff et al.,2003).***

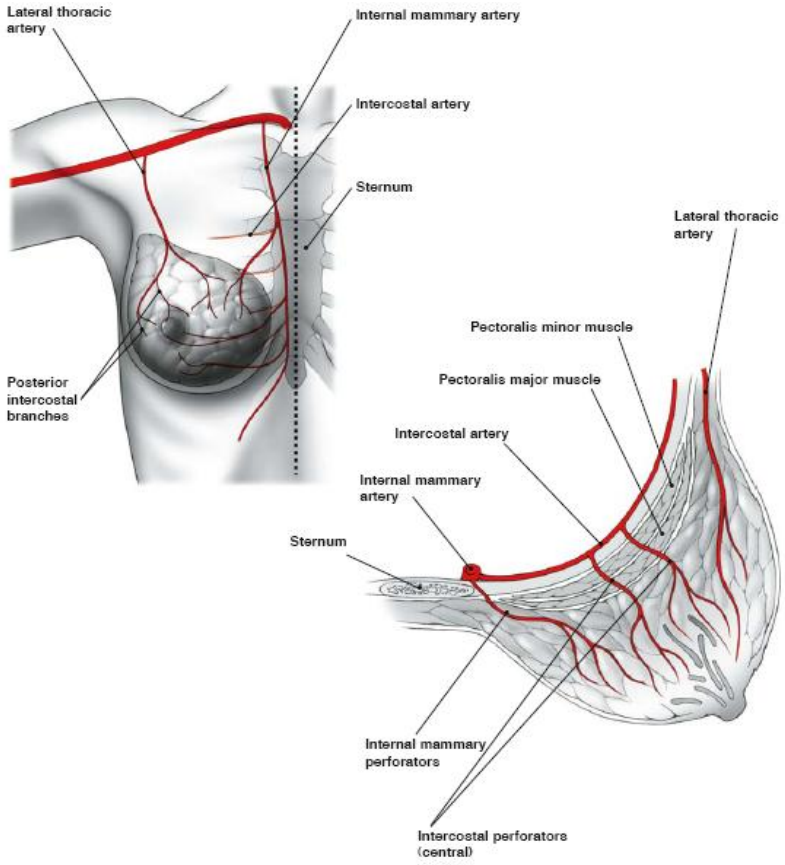


**Fig.:(3):** Arterial supply ***(Ismail et al.,2006).***

## ***Venous drainage:***

There is a circular venous plexus around the areola. From this, and from the glandular tissue, blood drains in veins which accompany the corresponding arteries that supply the breast ***(Johnson et al., 2008).***

The axillary, internal thoracic, and the third to fifth intercostal veins drain the mammary gland. These veins follow the arteries. The perforating tributaries from the medial half of the breast carry the greater part of the venous drainage. They enter the internal thoracic vein, which joins the

brachiocephalic vein. The axillary vein is formed by the junction of the basilic and brachial veins. It lies medial or superficial to the axillary artery and receives one or two pectoral branches from the breast. As it crosses the lateral border of the first rib, the axillary vein becomes the subclavian vein. The intercostal veins communicate posteriorly with the vertebral venous system, which enters the azygos, hemiazygos, and accessory hemiazygos veins, which in turn drain to the superior vena cava. Anteriorly, they communicate with the brachiocephalic vein by way of the internal thoracic veins. By the first two pathways, metastases of the breast readily reach the lungs. By the third pathway, metastases may travel to the skeleton and the central nervous system ***(Skandalakis et al., 2006).***

## ***Nerve supply to the breast:***

The second to sixth intercostal nerves supply breast innervation. Lateral innervation is predominantly from the anterior rami of lateral cutaneous branches of the third to the sixth intercostal nerves. Medial innervation arises from the anterior cutaneous branches of the second to the sixth intercostal nerves. Nerve supply to the nipple is from the third, fourth, and fifth anterior and lateral cutaneous nerves. The fourth intercostal nerve is the most important nipple innervator ***(Skandalakis et al., 2006).***

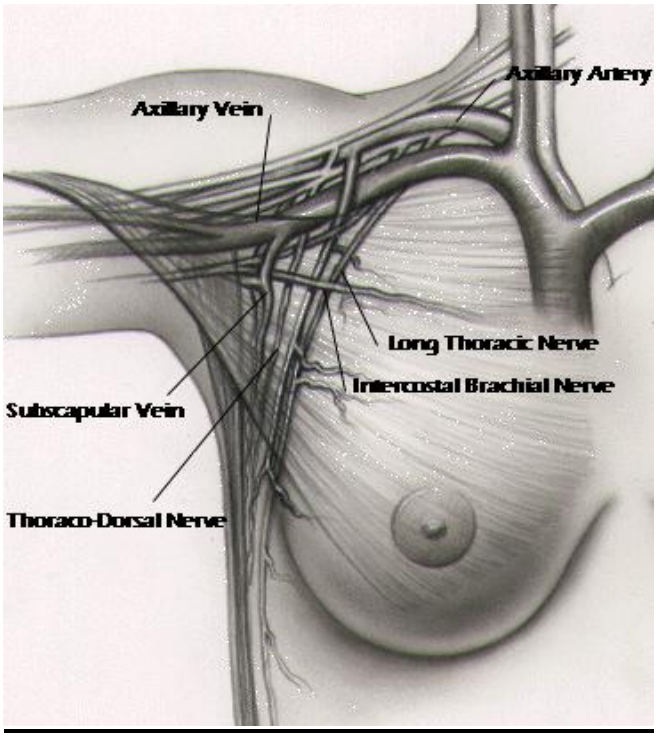


**Fig.: (4)** Nerve supply of the breast ***(Marisa et al., 2006).***

## ***Lymphatic Drainage:***

Current understanding of the lymphatic system of the breast is derived mainly from the work of the anatomist Sappey in the 1850 ***(Hiroo et al., 2007).***

### *The major groups of Haagensen are:*

1) Axillary 2) Internal thoracic (mammary) ***(Haagensen et al., 1972).***

### *Axillary Drainage:*

***Group 1****:* External mammary nodes, also called the anterior pectoral nodes. These lie along the lateral edge of the pectoralis minor, deep to the pectoralis major muscle, along the medial side of the axilla following the course of the lateral thoracic artery on the chest wall from the second to

the sixth rib. Deep to the areola there is an extensive network of lymphatic vessels, the so-called subareolar plexus of Sappey. In the circumareolar region, large lateral and medial trunks receive much of the lymph from the breast parenchyma. The lateral trunk receives collaterals from the upper half of the breast and the internal trunk drains the lower part of the breast. These vessels pass around the lateral border of the pectoralis major muscle to reach the external mammary nodes.

***Group 2:*** Scapular nodes. These lie on the subscapular vessels and their thoracodorsal branches. Lymphatics from these intercommunicate with intercostal lymphatic vessels.

***Group 3:*** Central nodes. This is the largest group of lymph nodes; they are the nodes most easily palpated in the axilla, because they are generally larger in size. They are embedded in fat in the center of the axilla. When these nodes enlarge, they can compress the intercostobrachial nerve, the lateral cutaneous branch of the second or third thoracic nerve, causing accompanying pain.

***Group 4:*** Interpectoral nodes (Rotter's nodes). These lie between the pectoralis major and minor muscles. Often there is a single node. They are the smallest group of axillary nodes and will not be found unless the pectoralis major is removed.

***Group 5:*** Axillary vein nodes. This is the second largest group of lymph nodes in the axilla. They lie on the caudal and ventral surfaces of the lateral part of the axillary vein.

***Group 6:*** Sub clavicular nodes. These lie on the caudal and ventral surfaces of the medial part of the axillary vein ***(John et al., 2006).***

Haagensen considered them to be inaccessible unless the pectoralis minor muscle is sacrificed ***(Haagensen et al.,1972).***

***Internal Thoracic (Mammary) Drainage***

Lymphatic vessels emerge from the medial edge of the breast on the pectoralis fascia. They accompany the perforating blood vessels, which, at the end of the intercostal space, pierce the pectoralis major and intercostal muscles to reach the internal thoracic nodes. These nodes also receive lymphatic trunks from the skin of the opposite breast, the liver, the diaphragm, the rectus sheath, and the upper part of the rectus abdominis. The nodes, about four to five on each side, are small and are usually in the fat and connective tissue of the intercostal spaces. The internal thoracic trunks empty into the thoracic duct or the right lymphatic duct. This route to the venous system is shorter than the axillary route ***(John et al., 2006).***

Since dissection of the internal mammary nodes is not done today, Scatarige et al. advised lateral chest radiography, computed tomography, high-resolution sonography, magnetic resonance imaging, and radionuclide lymphoscintigraphy ***(Scatarige et al.,1990).***

The breast lymphatics drain by way of three major routes: axillary, transpectoral, and internal mammary. Intramammary lymph nodes are considered with, and coded as, axillary lymph nodes for staging purposes; metastasis to any other lymph node is considered distant (M1), including supraclavicular, cervical, or contralateral internal mammary. The regional lymph nodes are presented here:

1. ***Axillary (ipsilateral):*** Interpectoral (Rotter's) nodes and lymph nodes along the axillary vein and its tributaries that may be (but are not required to be) divided into the following levels*:*