Hormones, Sex Hormone Binding Globulin And Abnormal Proliferative States In Gynaecology

THESIS

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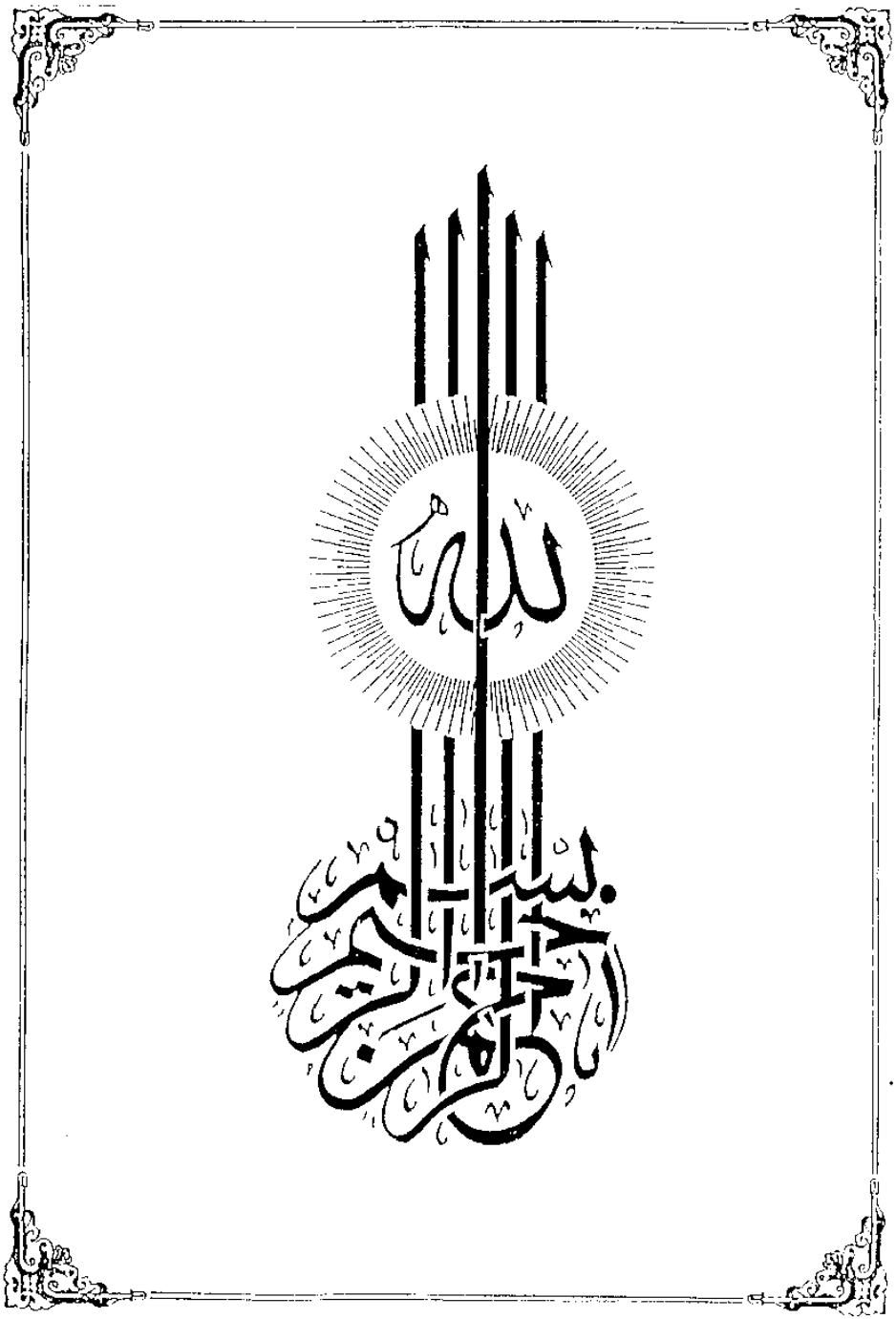

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Terminology of Endometrial Hyperplasia :

Little controversy exists about the usage of the term "cystic-glandular hyperplasia" for the very common form of swiss-cheese hyperplasia, that is clearly related to continous unopposed estrogen stimulation (Scully 1982).This term has been occasionally confused in the earlier literature with " cystic atrophy of the endometrium" (Scully 1982).The latter is a common pattern in elderly women and is characterized by glands with a predominantly flattened epilthelium and by a fibrotic stroma.

In contrast, there has been considerable disagreement about the terminology of the more important complex hyperplasia, which involve alterations on the pathway to carcinoma both in the architecture and proximity of the glands and in their lining epithelium.

Much of the present day confusion about the significance of the various forms of complex hyperplasia stems from differing interpretations of the widely used terms " adenomatous hyperplasia " , " atypical hyperplasia " , and " carcinoma in situ " .
Gusberg (1947) introduced the term adenomatous hyperplasia to include the entire spectrum of precancerous architectural and cytologic abnormalities

of the endometrium with the exception of cystic hyperplasia. Hertig and associates (1949) subsequently restricted the scope of this term to mild and moderate forms of architectural and cytologic atypia. The investigators also introduced the designation anaplasia (now rarely used) for a precancerous lesions of a higher grade of severity characterized by variation in the size, shape and staining of the nuclei and cytoplasm as well as loss of cellular polarity. Campbell and Barter (1961) have described anaplasia as " atypical hyperplasia " (type II or III).

The most severe lesions within the Gusberg spectrum of adenomatous hyperplasia was called carcinoma in situ and was defined as a focus of crowded glands lined by large cells that are often stratified, vary in size and lack normal polarity, with abundant cytoplasm and pale nuclei.

The older term " atypical hyperplasia " has been used by many authors as a synonym for Gusberg's adenomatous hyperplasia, but Wentz (1966) and subsequently Vellios and associates (1964, 1974) altered the usage of these terms, so that the latter indicates abnormalities in the architecture of the glands and the former represents epithelial dysplasia.

Still other authors have used the term " atypical adenomatous hyperplasia ", presumably to refer to a combination of cytologic and architectural atypicality, but have not defined the designation precisely (Scully 1982).

Relation Of Hyperplasia To Adenocarcinoma

Until recent years have been inclined to deny to hyperplasia any such predisposing influence in the development of cancer (Novak and Martzloff 1924). Similar opinions have been expressed by numerous other writers (Cullen 1900, Schroder 1915, Schaw 1929, and Burch 1936). Although Mayer (1923) and Taylor (1932) have reported cases in which adenocarcinoma had developed in uteri which were the seat of hyperplasia. An excellent study of the relation of hyperplasia to adenocarcinoma was made in 1932 by Taylor, who presented evidence that hyperplasia may be a predisposing factor in the later development of cancer.

Novak(1936) changed his idea and reported twenty five cases of endometrial hyperplasia co-existing with carcinoma of the endometrium and he expressed the belief that postmenopausal hyperplasia is a premalignant lesion.

It has been established both clinically and experimentally that cystic hyperplasia is a tissue effect of excessive estrogen stimulation (Salmi 1980). Also evidence pointing to estrogen as a cause of endometrial cancer is available (Gusberg 1967, Lucas 1974, Siiteri 1974, Gordan 1976, and Hertz 1976).

Lucas (1974) also remarked that the possibility of prolactin as etiologic factor should be considered, evidence has been forwarded that estrogens stimulate prolactin secretion (Neil 1974).

Forsberg and Breistein (1976) reported on the synergistic effect of estradiol and prolactin in influencing the incidence of 3-methylcholantherene induced cancer in the uterine cervix of castrated mice.

Prospective studies have shown that cystic hyperplasia has a rather low cumulative risk of developing endometrial carcinoma, 0.4% (Mc Bride 1959). Endometrial carcinoma is accompanied by adenomatous hyperplasia in 8% to 25% of cases (Salmi 1980). Various figuers are given in the literature for the progression from adenomatous hyperplasia to endometrial carcinoma, evidently because the different follow-up times, the mean is 18% (Gusberg et al., 1974).

Wentz (1974) reported the follow up of 145 women with untreated adenomatous hyperplasia, atypical hyperplasia, and adenocarcinoma in situ for periods of 2-8 years.Twenty-seven percent of those with adenomatous hyperplasia, and all those with adenocarcinoma in situ subsequently had carcinoma of the endometrium.

Sherman and Brown (1979) followed up for 2-18 years 216 untreated women with one or another form of complex

hyperplasia of the endometrium. They found that 22% of those with adenomatous hyperplasia, 57% of those with atypical hyperplasia, and 59% of those with carcinoma in situ, subsequently developed adenocarcinoma of the endometrium. In addition to progressing to cancer in a proportion of the cases, adenomatous hyperplasia remained the same or changed to a more severe precancerous lesion in 49% of the cases,to atypical adenomatous hyperplasia in 32% of the cases carcinoma in situ in 8%.

Introduction

Introduction

For many years there has been a relative lack of interest in endometrial cancer by oncologists because of its apparently low incidence, relatively low virulence and correspondingly low mortality rate relative to other cancers.

The interest in this tumour started to increase with a realization that it could be a hormonally dependent malignancy. Thus studies in humans started to establish the relation of the powerfull mitotic stimulant, estrogen, to the onset of the tumour.

An association between endometrial hyperplasia and subsequent carcinoma was first noted by Backer in 1904. The reveiw by Taylor (1932), suggested that a definite correlation between these entities did exist and furthermore, that estrogenic substances might, under certain circumstances be carcinogenic.

Novak and Yui (1936) felt that the simultaneous occurance of endometrial hyperplasia and endometrial carcinoma was a coincidence rather than an indication of fundamental relationship between the two. However, these investigators found it necessary to change this concept later. They indicated that hyperplasia persisting after the menopause predisposes to the development of endometrial carcinoma.

The relationship between hormones and endometrial cancer has been the subject of investigations for many years and has been reviewed by a number of ivestigators (Larson 1954 ; Andrews 1961 and Gusberg 1967).

Larson (1954), reviewed the literature relative to the relationship of estogens to endometrial carcinoma and was able to formulate five distinctly different points of view held by various groups of investigators. Briefly these are as follows :

1- Endometrial hyperplasia does not have any tendency towards malignant change in the reproductive years, but when it occurs as a result of postmenopausal estrogenic stimulation of the endometrium, it may predispose towards malignant disease.

2- Endometrial hyperplasia (and hence excess estrogen stimulation) predispose to carcinoma at any age.

3- Endometrial hyperplasia and cancer are not associated but the unopposed action of estorgen with its resultant effect on the endometrium, is the basic principle in the development of an endometrial carcinoma of those individuals who possess the genetic factor necessary for the development of cancer.

4- Endometrial hyperplasia may be followed by anaplasia, carcinoma in stiu, and adenocarcinoma of the uterus but, no convincing studies are available to show that estrogen stimulation alone will produce this picture.

5- Neither hyperplasia nor prolonged estrogen stimulation is associated with endometrial cancer other than an a chance basis.

Estrogen stimulation of the endometrium unopposed by progesterone can produce a progression of changes from benign proliferation to atypical hyperplasia and adenocarcinoma of the endometrium (Gusberg, 1967).

MacDonald and Siiteri (1974), have suggested that women at high risk for endometrial carcinoma have either a high proportion of estrogen precursors (androstenedione and DHA-S) in the plasma due to cystic ovarian syndorme with infertility or ovarian stromal hyperplasia, or an increase conversion rate from plasma estone precursors to estrone.

The degree of extraglandular estrogen formation has been related to the development of endometrial carcinoma. After the menopause the estrogen production can be totally accounted for by the circulating androstendedione, there being no evidence of direct ovarian and adrenal secretion. (MacDonald et al., 1968; Gordin et al., 1973 and MacDonald & Siiteri 1974).

Many studies conducted in the past showed that obesity, diabetes mellitus, hypertension, infertility/nulliparity, late menopause, high endogenous estrogen production and the use of estrogen are the main factors associated with the development of endometrial carcinoma (Tuula Salmi 1980).

One of the well documented effects of estorgen on the endometrium is its growth stimulating effect with resultant hyperplasia (Gamberell, 1983).

Much of the present day confusion about the significance of the various forms of hyperplasia stems from differing interpretation of the widely used terms "adenomatous hyperplasia ", " atypical hyperplasia" and "carcinoma in situ ".

Gubserg introduced the designation " adenomatous hyperplasia " in 1947 to include the entire spectrum of precancerous architectural and cytologic abnormalities of the endometrium with the exception of cystic hyperplasia.

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