"HORMONE SECRETION BY SO-CALLED FUNCTIONALLY INACTIVE OVARIAN TUMOURS"

(A Review)

by

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There is definite evidence that ovarian tumours, other than those commonly regarded as hormonally active, do, in fact, produce hormones. In this category of tumours are cystadenomas, Brenner tumours and certain ovarian carcinomas. Most of these new growths are not associated with apparent endocrine effect in the vast majority of cases and, therefore, they are regarded by most authorities as non-functionating. Occasional occurrence of endocrine changes is dismissed as strange coincidence. The present paper is an attempt to review this group of ovarian neoplasms from the available current medical literature (including a published case of the author).

Brenner Tumour

This tumour is usually unassociated with endocrine anomalies. The view expressed by Novak and Novak (1958) that these tumours do not have any hormonal influence is the one generally accepted. Occasionally, however, endocrine manifestations have been recorded (Farrar et al., 1960). Although most authorities are not impressed by any association of Brenner tumours with endocrine changes, abnormal uterine bleeding has been reported in 25 per cent of cases in several series (Bland et al., 1935, Jondahl et al., 1950; Novak et al., 1939; Teoh 1953). Teoh (1953) described abnormal bleeding in five out of a series of ten patients. One of Teoh's cases had endometrial hyperplasia, and the stroma of the tumours contained lipoid and resembled a thecoma. Endometrial hyperplasia has been observed in approximately 10 per cent by Biggert et al., (1955), Jondahl et al., (1952) and Teoh (1953). Biggert and his colleagues (1955) reported three cases of uterine bleeding in his series of 15 Brenner tumours and two of these uterine bleedings were in postmenopausal women with endometrial hyperplasia. Abnormal uterine bleeding, almost always postmenopausal, has also been noted in association with Brenner tumours by others (Andujar et al., 1947; Eton et al., 1958; Mackinlay et al., 1956; Ming et al., 1962; Morris and Scully 1958; Woodruff 1962). Some authors (Biggert et al., 1955) attributed the

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endometrial hyperplasia to hormones probably liberated by the thecoma-like stroma (rich in doubly refractile fat) of the Brenner tumour, as the thecoma-like stroma was conspicuous by its absence in cases of Brenner tumour unassociated with uterine bleeding. Postmenopausal enlargement or tenderness of the breasts has been described (Gryzel et al., 1941; Marwill et al., 1942; Tighe, 1961). Three patients of Tighe's series (Tighe 1961) presented interesting features, possibly related to oestrogen stimulation. One woman stated that she also had sickness of such severity that she thought she was pregnant (although she had postmenopausal amenorrhoea for 2 years). At laparotomy this woman was found to have an ovarian dermoid cyst as well as a Brenner tumour.

Adeno-carcinoma of the endometrium associated with Brenner tumour has also been reported (Eton et al., 1958; Farrar et al., 1960; Jondahl et al., 1950; Mackinlay et al., 1956; Ming et al., 1962; Shaaban et al., 1960; Teoh 1953; Tighe 1961; Woodruff 1962, Shay and Janovski 1963); and a casual relationship of adenocarcinoma with abnormal oestrogen production has been recognised. Shaaban et al., (1960) found increased urinary oestrogen level in his reported case of Brenner tumour in a postmenopausal woman with adenocarcinoma of the corpus uteri, metropathia haemorrhagica, adenomyosis uteri and fibroma of the uterus.

Sufficient evidence is, therefore, available to suggest strongly that a certain percentage of Brenner tumours have functionally active stromal element producing oestrogens.

Krukenberg Tumour

Recently, there is some evidence on Krukenberg tumours producing hormones. Truenen (1955) reported two cases of Krukenberg in postmenopausal women, and claimed that this is associated with endometrial hyperplasia and abnormal uterine bleeding more often than other supposedly inactive ovarian tumours. The author attributes the uterine changes to the secretion by the 'theca-like stroma' which is occasionally associated with the Krukenberg tumour.

Pseudo-mucinous Cystadenoma

Masson (1938) has demonstrated that the majority of pseudo-mucinous cystadenoma contain argentiform cells providing opportunities for carcinoid development. This, by liberating 5-hydroxy-tryptamine, produces the typical features of dyspnoea, asthma, flushing and arterial hypertension (Valsecchi 1954; Spies and Stone 1952). Banerji (1964) reported a case of a pseudo-broad ligament cyst of the ovary with the histological picture of pseudo-mucinous cystadenoma associated with hypertension, erythrocytosis and Meigs syndrome; these clinical features disappeared after removal of the tumour. He suggested that liberation of erythropoetin-like substance by the tumour was responsible for the erythrocytosis and probably tiny areas of argentiform cells were responsible for the clinical features of carcinoid tumours.

Dysgerminoma

Dysgerminoma, supposedly arising from sexually undifferentiated mesenchymal cells of the early gonad, is believed to be hormonally inactive. However, there is a high association of these tumours with sexual underdevelopment and pseudo-hermaphroditism. It has been suggested that this tumour is capable of inhibiting normal feminine development (Gough 1949), while others state that it is inactive. Scully (1953) thinks that the absence of hormonal effect is in keeping with the neutral character of the undifferentiated cells particularly in its histogenic formation.

In the majority of cases, no cause-effect relationship exists between ovarian germinomas and sexual abnormalities with which they are often associated. In a few instances precocious sexual development (Hain 1949) or masculinizing manifestations (Gough 1949; Saegar 1938) have regressed after removal of the tumour. Some degree of virilism frequently accompanies "dysgerminoma". Giushi et al., (1962) reported a clinical, histological and hormonal study of ovarian dysgerminoma with precocious iso-sexual puberty followed by virilization.

The reported absence of hormonal secretion is not a constant observation. Elevated gonadotrophin levels have been reported (Burge 1949; Potter 1946; Moreton 1947; Santeson 1947). These are probably produced by chorion-epitheliomatous elements frequently present in dysgerminoma (Melicome, 1959) but this association has not always been confirmed by microscopic study either in ovarian mesenchyme or testicular germinoma.

Fibro-thecoma of Ovary with Stromal Neoplasia

Willis (1960) has suggested that many if not all fibromas of the ovary are really "fibrous theca cell tumours". Sternberg and Gaskill (1950) recognised the association of fibroma, thecoma and stromal hyperplasia. Daley and his colleagues (1950) proposed a concept that this kind of fibrous tumours of ovary produces oestrogens; the association of cystic endometrial hyperplasia and ovarian cystfibro-adenoma in a 61 year old patient with postmenopausal bleeding was in support of this concept. Sharman and Sutherland (1947) reported abnormal uterine bleeding in association with the lesions.

Morrison and Woodruff (1964) studied 104 ovarian tumours composed largely of stroma with or without cystic and adenomatous elements; and evaluated the endometria particularly in postmenopausal patients for evidence of hormone stimulation. Although correlation of active endometria with theca-like changes in the ovarian tumour was not always accurate, there was enough evidence to suggest a definite relationship. Hughesdon (1963) described under "Misfit tumours" one type associated with anomalous functional effects. This type of tumour is not normally hormonally active, but may be so if a theca-lutein reaction develops in the stroma. This is commonest in primary carcinoma but can occur in a benign tumour and also in a secondary carcinoma. Hughesdon gave a

preliminary account in 1958. Out of 81 primary ovarian carcinoma, 16 showed marked stromal thecal reaction; and of the 9 uteri available for study 7 showed cystic endometrial hyperplasia and proliferative phase (Hughesdon 1963). Virilizing effects were not seen by him but others reported about it.

Beck and Latour (1962) found 13.9 per cent incidence of endometrial hyperplasia in the fibromas (as compared to 15 per cent in routine endometrial examination); and stressed the fact that the fibromas are probably not functional and the excess oestrogen stimulation of the endometrium was from a source other than the co-existing fibroma.

Comment

The ovary contains the widest range of cellular material in the body. It is the seat of most primitive cells, the germ cells. Therefore, it possesses the potentiality to develop into any of the tissue elements of the body. The possible endocrine effect of Brenner tumours has aroused interest in recent years. In view of this, it is probably important to investigate all patients with solid ovarian tumours with abnormal vaginal bleeding both by histological and hormonal study, as it is thus that any hormonal (oestrogenic) effects may be proved.

In addition to the capacity to produce gonadal hormones such as oestrogen, androgen and gonadotrophins from diversely differentiated tissues, it is interesting that ovarian tumours may develop carcinoid features as in pseudo-mucinous cystadenomas (Banerji 1964; Mason 1938), in benign dermoid cyst (Mitchel and Diamond 1949) and in masculinizing arrhenoblastoma (Hartz 1945). The suggested possibility of producing erythropoetin-like substance (Banerji 1964) deserves further critical study. The manifestation of hormonic effect by Krukenberg (Truenen 1955), an otherwise hormonally inactive tumour, demands further observation. Adeno-fibromas or fibrothecomas require further search of hormone potentiality. It is in the study of this new group of tumours that a closer team work of gynaecologists, histologists, endocrinologist and biochemists is so essential.

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