OESTROGENIC ACTIVITY ASSOCIATED WITH NON-FEMINIZING OVARIAN TUMOURS AFTER THE MENOPAUSE

BY

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The fact that a certain group of ovarian tumours produce considerable quantities of oestrogen has been known for some time. However, it is only recently that the suggestion that all ovarian tumours may produce increased levels of oestrogen has been put forward.

In this article we have reviewed 80 consecutive cases of post-menopausal ovarian tumour admitted to the gynaecological department at Hammersmith Hospital. Exfoliative cytology and histopathology were employed in the assessment of oestrogen function. The cases were collected from the years 1954 to 1962 inclusive and reviewed to exclude any exogenous source of oestrogen or other hormone which might have had some effect on the reproductive tract.

Oestrogenic influence was assessed by two indirect methods, which were: (a) the cornification index in the vaginal smear, and (b) histological examination of the endometrium.

Vaginal Smear and Cornification Index

Exfoliative vaginal cytology is the study of cells which desquamate from the vaginal or cervical epithelium. Evaluation of hormone effects on these exfoliated cells collected from the posterior vaginal fornix has been described by various authors (de Allende and Orias, 1950; Pundel, 1950; Wachtel and Plester, 1954).

Three types of squamous cells appear in the posterior fornix pool: parabasal cells, which are the least mature, and intermediate and superficial cells, the last being the most mature. Some of the superficial squamous cells have dark structureless nuclei, known as pyknotic nuclei, not more than 6 microns in diameter. The cornification index (C.I.) is a simple count of cells with pyknotic nuclei expressed as a percentage of all the superficial and intermediate squamous cells present. It is this index which mirrors the effect of oestrogenic substances on the vagina. In general, the higher the C.I. the greater the oestrogenic effect.

The C.I., however, may be affected by factors other than hormones—for example, inflammation, nutrition, etc. A paper by one of us (J. F.), in preparation, examines these factors, and attempts to explain the rise in C.I. in the older age-groups of women past the menopause. The present article is concerned with the oestrogenic effect in the vaginal smears of post-menopausal women with ovarian tumours.

Review of Literature

The function of the ovary in the menopause has long been a controversial subject, but the general weight of opinion has tended to show that after the menopause the ovaries cease to produce significant quantities of oestrogen and that increased levels of oestrogen are produced only by certain ovarian tumours.

Struthers (1956), using vaginal cytology as an indicator of oestrogenic activity, reviewed 353 women in the post-

menopausal age-group for evidence of oestrogen function. He showed that some oestrogenic function is present in at least 50% of post-menopausal women, and good oestrogen function appeared to be present in 5% of these women. In only 20% of his series of cases could he find complete absence of any oestrogenic activity. To show that this oestrogen was probably not derived from the ovary he included 243 women in his series who had either a surgical or radiation menopause and found the same distribution of oestrogen activity. He supposed the source of the oestrogen to be from some other organ than the ovary, but not necessarily the adrenal.

Brown, Kellar, and Matthew (1959) investigated, by bio-assay, oestrogenic compounds in 23 cases of post-menopausal bleeding. They showed that in 10 cases where some endometrial pathology was the sole source of the bleeding oestrogenic hormone levels were low and insufficient to stimulate the endometrium. They also supposed that the source of this oestrogen was not from the ovary but probably from the adrenal cortex. They showed seven cases of post-menopausal bleeding where high levels of oestrogen were present, sufficient to stimulate the growth of a proliferative endometrium and cystic glandular hyperplasia. In three of these seven cases an ovarian tumour was present (pseudomucinous cystadenoma; adenocarcinoma; theca-granulosa cell tumour). The surgical removal of these tumours led to a fall in the levels of oestrogenic hormone.

Novak (1956) reviewed 36 cases of post-menopausal endometrial hyperplasia where a full pathological survey of ovarian tissues could be carried out. He found that 22% of cases were associated with some form of ovarian tumour. However, half these tumours were of the known feminizing variety, but there still appeared to be a greatly increased association between the presence of non-feminizing tumours and endometrial hyperplasia.

Greene (1957) stated that he had examined the uteri of 335 normal women who had a hysterectomy at least two years after the menopause. In his investigation only 4 of these 335 women showed any evidence of endometrial proliferation (3 had hyperplasia, 1 had proliferation). He stressed that the specimens were obtained from *normal* post-menopausal women.

Novak and Williams (1960) showed that after ovarian castration there is no clinical or pathological evidence for any increase in atherosclerosis or osteoporosis, regardless of age of operation performed. This again suggests that the ovary normally does not play any significant part in the production of oestrogens after the menopause.

From a review of the literature, then, it would appear that ovaries cease to produce significant quantities of oestrogens after the menopause and that the low levels found are probably produced by some organ other than the ovary. The adrenal has not been definitely implicated as the sole source of oestrogen production. The oestrogen is derived from granulosa or theca cells, and so it is reasonable to suppose that when follicle formation ceases an important source of oestrogen disappears. There are some post-menopausal women who have high oestrogenic

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hormone levels, proliferative endometrium, and some pathological condition in the ovary. In a large number of such women the lesion in the ovary is neoplastic, but not necessarily a known feminizing tumour.

Method of Collection of Material

Every patient attending the gynaecological clinic has a vaginal smear taken as a routine. These smears were examined and reported on by only two people during the eight-year period. Sixty-four of the patients with ovarian tumours had a preoperative smear and C.I. available for review.

Endometrium obtained at diagnostic curettage or from hysterectomy specimens is submitted for histological examination. Fifty-four cases in the series had endometrium available for pathological examination for evidence of proliferative or hypertrophic endometrium.

Results

Table I shows the results of analysing over 500 post-menopausal vaginal smears by one of us (J.F.). None of these cases had demonstrable ovarian tumours. The group was divided into five-year sections by age. In each vaginal smear the C.I. was evaluated. The table shows in different age-groups that between 67 and 85% of the preparations had a C.I. of 4 or below.

TABLE I.—Control C.I. by Age-groups

Ages	No.	Cornification Index		
		0-4	5-9	10+
Up to 50	219	147 (67.1%)	53	19
51-55	114	87 (76.3%)	20	7
56-60	81	69 (85.2%)	9	3
61-65	78	54 (69.2%)	15	9
66+	78	55 (70.5%)	18	5
Total	570	412 (72.3%)	115	43

Table II shows a large number of observations arranged in time intervals since the menopause occurred. Here again, in differing five-year intervals, it is seen that between 64 and 87% had a C.I. of 4 or below. Arbitrarily, therefore, it was decided that preparations with a C.I. of 5 or above showed a moderate to marked oestrogen effect. Tables I and II show that between 13 and 36% of the control series exhibit a moderate to marked oestrogen effect defined in this way.

TABLE II.—Control C.I. by Years Since the Menopause

Years since Menopause	No.	Cornification Index		
		0-4	5-9	10+
1-5	290	211 (72.8%)	52	27
6-10	98	84 (85.7%)	10	4
11-15	82	71 (86.6%)	7	4
16-20	74	55 (74.5%)	11	8
21+	139	89 (64%)	40	10
Total	683	510	120	53

Table III lists the patients with ovarian tumours by age in five-year intervals and compares their C.I. with the C.I.s

TABLE III.—Ovarian Tumours—Age-groups

Ages	No.	No. with C.I. Available	Cornification Index				Control with C.I. of 5+
			0-4	5-9	10+	5+	
Up to 50	12	10	3	3	4	7 (70%)	72 (32.9%)
51-55	16	12	6	5	1	6 (50%)	27 (23.7%)
56-60	17	11	4	3	4	7 (63.6%)	12 (14.8%)
61-65	14	12	8	2	2	4 (33.3%)	24 (30.8%)
66+	21	19	7	7	5	12 (57%)	23 (29.5%)
Total	80	64	28	20	16	36 (56.3%)	158 (27.7%)

found in the control group in Table I. There were 64 tumour patients who had a cytological examination made. The figures suggest that at least twice as many patients with ovarian tumours have a raised C.I. as do the control series. The difference between these two groups is highly significant ($P < 0.001$).

In the groups with a C.I. of 10 or over the presence of higher quantities of oestrogen appeared to be found three times more often in the tumour group (25%) than in the control group (7.5%).

Table IV lists the patients with ovarian tumours by five-year intervals past the menopause and compares them with the similar controls in Table II. The pattern of oestrogenic influence, as indicated by the C.I., is similar to that expressed in Table III. The difference between these two groups is highly significant ($P < 0.001$). Table V summarizes the foregoing results for easier comparison.

TABLE IV.—Ovarian Tumours—Years Since Menopause

Years from Menopause	No. Tumours	No. with C.I.	Cornification Index				Control with C.I. of 5+
			0-4	5-9	10+	5+	
0-5	25	21	8	7	6	13 (61.9%)	79 (27.2%)
6-10	13	7	3	4	0	4 (57%)	14 (14.3%)
11-15	14	11	7	2	2	4 (36%)	11 (13.4%)
16-20	8	6	2	0	4	4 (66%)	19 (25.5%)
21+	19	19	8	7	4	11 (52.4%)	50 (36%)
Unknown	1						
Total	80	64	28	20	16	36 (56.3%)	173 (25.4%)

TABLE V

Cornification Index		0-4	5-9	10+
Tumours	..	28 (43.8%)	20 (31.3%)	16 (25.0%)
Controls	..	412 (73.2%)	115 (20.2%)	43 (7.5%)
		510 (74.6%)	120 (17.5%)	53 (7.9%)

Table VI sets out the various types of ovarian tumour and those among them that showed some oestrogen function, as evidenced by the C.I. From this table it is seen that oestrogenic function seems to be about three times as common in women with serous cystadenomas as in the control group.

TABLE VI.—Ovarian Tumours—Activity by C.I.

Tumours	No. of Tumours	Tumours with C.I. Available	C.I.			Tumours with C.I. 5+
			0-4	5-9	10+	
Serous cystadenoma	18	15	4	6	5	11 (73.3%)
Pseudomucinous cystadenoma	19	19	9	6	4	10 (52.6%)
Adenocarcinoma	33	22	11	5	6	11 (50%)
Feminizing tumour	5	3		2	1	3 (100%)
Masculinizing tumour	1	1	1			
"Neutral" tumour	4	4	3	1		1 (25%)
Total	80	64	28	20	16	36 (56.3%)

Oestrogenic activity is twice as common in pseudomucinous cystadenomas and adenocarcinomas as in the control group. Feminizing tumours all showed a high oestrogenic pattern, whereas only one of the four "neutral" tumours (a dysgerminoma) showed oestrogenic activity—the same percentage as found in normal controls.

Table VII presents other evidence of oestrogen activity, and this is tabulated according to the type of tumour. In these tumours, where endometrium was examined histologically, it can be seen that about 40% of the three common types of ovarian tumour showed evidence of active endometrium, suggesting increased oestrogen levels.

Post-menopausal bleeding was another common symptom occurring in 31% of patients with an ovarian tumour but being particularly common in those women with serous cystadenomas (44%).

TABLE VII.—*Ovarian Tumours—Activity by Endometrial Response*

Tumours	No. of Tumours	Endo- metrium Exam- ined	Active Endo- metrium	Active Endo- metrium and C.I. of 5+	Post-menopausal Bleeding		
					History of	And Active Endo- metrium	And C.I. of 5+
Serous cyst- adenoma	18	15	6 (40%)	5	8	4	5
Pseudo- mucinous cyst	19	16	6 (37.5%)	2	5	3	3
Adeno- carcinoma	33	15	6 (40%)	4	7	1	2
Feminizing tumour	5	4	3 (75%)	1	5	2	3
Masculin- izing tumour	1	1	1 (100%)				
Neutral tumour	4	3	1 (25%)	1			
Total	80	54	23 (42.6%)	13	25 (31.2%)	10	13

Discussion

Evidence has been presented that normal post-menopausal women secrete oestrogen in low quantities, but probably not from the ovary. The C.I. is 4 or below in 75% of these women, and evidence presented suggests that the endometrium is inactive in 99% of normal post-menopausal women.

In our series of 80 ovarian tumours found in post-menopausal women we found evidence of increased oestrogen production in over half of these cases, as measured by the C.I. In the 54 cases where endometrium was available, active proliferation or cystic hyperplasia was present in 40%. This contrasts markedly with Greene's series of slightly more than 1% endometrial activity in normal post-menopausal women.

Post-menopausal bleeding occurred in over 30% of our cases with ovarian tumour, and suggests that some hormonal effect may have been present.

It is suggested that the oestrogen in these tumours is derived from cells of the granulosa-theca type which persist in the post-menopausal ovary or develop with the growth of the tumour. It might be that these tumours develop from ovaries which, though macroscopically normal, produce elevated levels of oestrogen before progressing to tumour formation.

These ovaries would probably be found among those apparently normal post-menopausal women with elevated C.I.s.

It appears that of the three major types of ovarian tumour in this series the serous cystadenomas produce oestrogen more commonly than any other.

Unfortunately, biochemical methods of oestrogen estimation were not available for this study. Prospective studies of ovarian tumours from post-menopausal patients should include direct measurement of oestrogen levels.

Summary

A review of the literature on oestrogen production in post-menopausal women is presented, and evidence suggests that normally the ovary ceases functioning after the menopause, and that the low levels of oestrogen found are derived from some other organ, probably the adrenal.

A series of 80 consecutive ovarian tumours in post-menopausal women has been reviewed for evidence of oestrogen function, the presence of oestrogen being determined by the cornification index and/or endometrial activity.

Using the C.I. as an indicator of oestrogenic function, it appears that increased levels of oestrogen are found twice as commonly in post-menopausal women with an ovarian tumour as in normal post-menopausal women.

Ovarian tumours are associated with endometrial activity in 40% of cases subjected to histological examination, whereas in normal post-menopausal women endometrial activity is found in about 1% of cases.

Serous cystadenomas appear to have greater oestrogenic function than other types of the so-called non-feminizing ovarian tumours.

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IMIPRAMINE POISONING IN CHILDHOOD

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Imipramine ("tofranil") is an iminodibenzyl derivative chemically related to the phenothiazine series which is widely used for the treatment of depression in adults. Its many potential side-effects have been extensively documented (Azima and Vispo, 1959; English, 1959; Foster and Lancaster, 1959; Fullerton and Boardman, 1959; Mann, Catterson, and Macpherson, 1959; Segal and Howarth, 1960; Curran and Barabas, 1961), and the dangerous and sometimes fatal consequences of overdosage are well recognized (Brooke and Weatherly, 1959; Lancaster and Foster, 1959; Levene and Lascelles, 1959; Mann, 1960; Lee, 1961). Nevertheless, it does not yet seem to be generally realized that in young children serious poisoning can be caused by relatively small doses of imipramine, or that the resulting clinical picture is remarkably characteristic, and in its fully developed form perhaps unique.

Case reports of childhood poisoning are few, and a search has revealed only three detailed descriptions (Arneson, 1961; Alajem and Albagli, 1962; Garrison and Moffitt, 1962), two short notes (Noack, 1960; Connelly and Venables, 1961), and the passing comment by Fruthaler and Snyder (1962) in a general review of childhood poisoning that their personal experience includes one fatal and one non-fatal case. Yet during one eight-month period in 1961–2 at least seven Birmingham children were accidentally poisoned with imipramine, one of them fatally, suggesting that this is in fact an important and increasingly