

## HORMONAL PROFILES IN POSTMENOPAUSAL WOMEN AFTER THERAPY WITH SUBCUTANEOUS IMPLANTS

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### Summary

Plasma hormones were estimated in 24 postmenopausal patients who had been castrated. Each was given a sub-cutaneous implant of either 100 mg or 50 mg of oestradiol, or 50 mg of oestradiol with 100 mg of testosterone, or 200 mg of testosterone. Plasma hormone estimations were repeated at two weeks, one month and then monthly for up to 12 months. Plasma follicle stimulating hormone (FSH) and luteinizing hormone (LH) concentrations were seen to fall at two weeks after all implants containing oestradiol. Plasma testosterone concentrations rose from a mean concentration of 1.0 nmol/l to 5.0 nmol/l and 6.7 nmol/l after implants of 100 mg and 200 mg of testosterone respectively. Implants containing oestradiol caused the pretreatment ratio of the concentrations of oestrone to oestradiol to change from 2:1 to 1:2. The implant of 100 mg of oestradiol caused the plasma oestradiol concentration to rise to a mean value of 602.3 pmol/l and those of oestrone to rise to 356.7 pmol/l. The more commonly used implants contain 50 mg of oestradiol and these caused the mean concentration of plasma oestradiol to rise to 346.7 pmol/l and oestrone to rise to 233.9 pmol/l. These values compare favourably with those attained after oral oestrogen therapy.

PELLETS of oestradiol, implanted into the fat of the abdominal wall or buttock, have been used for over 30 years to treat symptoms of the climacteric (Greenblatt and Suran, 1949), but the practice has never gained wide acceptance. The restricted use is possibly due to a fear that this route of administration may lead to unacceptably high levels of oestrogens in the peripheral circulation.

A few supporters of hormone therapy with implants use a combination of testosterone with oestradiol and advocate this method for patients with a uterus. Irregular or heavy bleeding from the endometrium is avoided by the oral admin-

istration of a progestogen for 5 to 10 days every month (Thom *et al*, 1979; Thom and Studd, 1980).

The value of implants containing oestradiol and testosterone in the treatment of symptoms associated with the climacteric—particularly the loss of libido, has been reported (Studd *et al*, 1977*a* and *b*). The purpose of this study was to determine the hormonal profiles of patients who had received implants containing either 50 mg or 100 mg of oestradiol or 200 mg of testosterone or a combination of both (50 mg of oestradiol plus 100 mg of testosterone).

## SUBJECTS AND METHODS

Twenty-four symptomatic women attending the Dulwich Hospital menopause clinic were studied after a full history was taken and a clinical examination performed. All had previously undergone hysterectomy and bilateral oophorectomy. None had contra-indications to oestrogen therapy and all were willing to undergo monthly venepuncture after the implantation of hormonal pellets. The physical characteristics of the patients are shown in Table I.

Peripheral venous blood (20 ml) was taken on two occasions separated by a week before implantation and then monthly for up to a year. All samples were taken between 1000 and 1200 hours. The plasma was separated in a centrifuge and stored at  $-15^{\circ}\text{C}$ . The concentrations of follicle stimulating hormone (FSH), luteinizing hormone (LH), oestradiol, oestrone and testosterone were measured in all samples by radio-immunoassay (Chakravarti *et al*, 1976 and 1979). The hormone pellets were inserted using local anaesthesia in the outpatient department. A 2 to 3 mm incision was made in the skin of the abdominal wall, about 3 cm above the inguinal ligament medial to the anterior superior iliac spine. A trochar and cannula was inserted into the subcutaneous fat parallel to the inguinal ligament and the appropriate pellets inserted into the cannula by means of sterile forceps after removal of the trochar. The pellets were pushed into the depth of the tract by an obturator. The instrument was removed and pressure applied to the wound and tract with sterile cotton wool for about 30 seconds to secure haemostasis. The small entry wound was covered with a plaster. Groups of six patients were given one of the

following regimens of treatment: (1) 100 mg of oestradiol; (2) 50 mg of oestradiol; (3) 50 mg of oestradiol plus 100 mg of testosterone; and (4) 200 mg of testosterone (Organon Laboratories Ltd). The concentrations of plasma FSH and LH were best described by the arithmetic mean and range, and the steroid hormones by the geometric mean and range.

## RESULTS

*Oestradiol (100 mg) implant*

The pellets containing 100 mg of oestradiol had a dramatic effect on the concentration of plasma FSH. Normal and premenopausal values were observed in all six patients within two weeks of implantation for seven months (Fig. 1). Table II shows that the mean concentration of FSH fell from  $86.1\text{ U/l}$  to  $20.6\text{ U/l}$  at two weeks and  $8.4\text{ U/l}$  at three months. The value remained below  $15\text{ U/l}$  until six months, and at 12 months it was  $61.4\text{ U/l}$ . The concentration of LH was also reduced, but less dramatically. There was little effect on the concentration of plasma testosterone. The concentration of plasma oestradiol showed a considerable elevation to  $602.3\text{ pmol/l}$  and a less marked increase in oestrone to  $356.7\text{ pmol/l}$ . This elevation persisted for seven months. Some patients proved to be very sensitive to the slight fall in concentration at four months and developed symptoms to suggest that the implant had disappeared.

*Oestradiol (50 mg) implant*

Figure 2 shows that the 50 mg pellets of oestradiol had a similar but less dramatic effect than the 100 mg pellets on the concentrations of

TABLE I  
*Physical characteristics of patients in each treatment group*

Treatment	Age (years)	Years since oophorectomy	Height (cm)	Weight before implant (kg)
Oestradiol, 100 mg	50.7 (46-59)	2.8 (1-5)	161 (155-170)	62.0 (48.2-87.5)
Oestradiol, 50 mg	48.5 (31-63)	3.5 (1-7)	161 (158-168)	60.5 (47.5-72.1)
Testosterone, 100 mg plus oestradiol, 50 mg	50.5 (40-55)	3.7 (1-5)	160 (155-169)	58.0 (46.6-75.0)
Testosterone, 200 mg	47.0 (40-56)	3.5 (1-5)	162 (153-170)	59.0 (45.5-75.1)

All values are given as means with range in parenthesis.

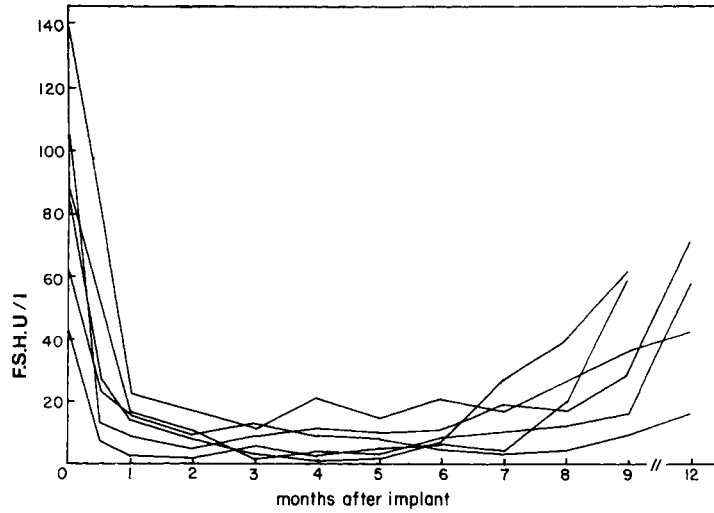


FIG. 1

The concentration of FSH in peripheral plasma from patients with an implant of oestradiol (100 mg).

TABLE II

The concentrations (mean and range) of various hormones in peripheral plasma before and after an implant of oestradiol (100 mg)

Time (months)	FSH* (U/l)	LH* (U/l)	Testosterone† (nmol/l)	Oestrone† (pmol/l)	Oestradiol† (pmol/l)
Before implant	86.1 (43.4-140.2)	52.8 (36.3-72.4)	1.3 (0.9-2.0)	76.1 (49.9-97.7)	46.7 (26.7-54.0)
0.5	20.6 (13.2-32.6)	28.1 (13.1-41.9)	1.7 (1.1-2.8)	190.2 (111.9-271.2)	279.9 (160.5-308.4)
1	13.0 (7.2-24.3)	21.5 (18.3-30.7)	1.9 (1.4-3.0)	266.5 (194.9-319.7)	359.5 (246.9-416.7)
2	10.2 (4.3-17.7)	17.4 (11.3-23.2)	2.3 (1.2-3.1)	352.6 (195.1-426.7)	583.7 (232.2-696.5)
3	8.4 (3.9-12.7)	15.6 (10.6-21.2)	2.2 (0.9-2.9)	356.7 (221.4-518.4)	602.3 (302.7-714.2)
4	8.4 (0.7-15.2)	20.1 (15.2-28.4)	2.0 (0.8-2.8)	271.7 (171.2-308.2)	592.1 (278.3-700.2)
5	10.8 (4.7-22.4)	24.0 (17.3-31.3)	1.8 (0.9-2.5)	260.3 (204.7-323.4)	352.7 (275.1-432.0)
6	16.0 (3.2-27.6)	32.3 (22.1-41.2)	1.8 (1.0-2.8)	214.0 (168.4-392.1)	376.2 (236.3-404.1)
7	20.3 (9.3-24.6)	37.4 (31.6-41.4)	1.8 (1.0-3.0)	272.2 (137.1-314.0)	392.7 (217.1-416.1)
8	30.7 (18.4-48.1)	44.8 (39.3-49.1)	1.8 (0.9-2.4)	259.2 (172.2-340.2)	269.3 (190.3-328.1)
9	38.3 (21.4-54.2)	49.3 (37.3-59.0)	1.5 (0.8-2.2)	217.3 (181.2-282.4)	222.7 (160.2-260.4)
12	61.4 (43.1-92.1)	55.3 (46.3-74.6)	1.1 (0.7-2.4)	203.4 (121.2-257.2)	201.9 (148.3-264.2)

\* Arithmetic mean.

† Geometric mean.

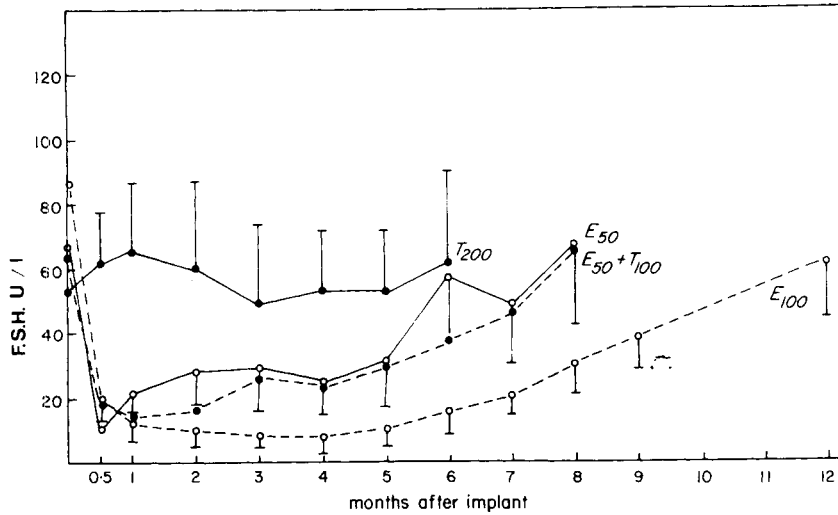


FIG. 2

The concentrations (mean and SE) of FSH in peripheral plasma from patients with various hormonal implants.

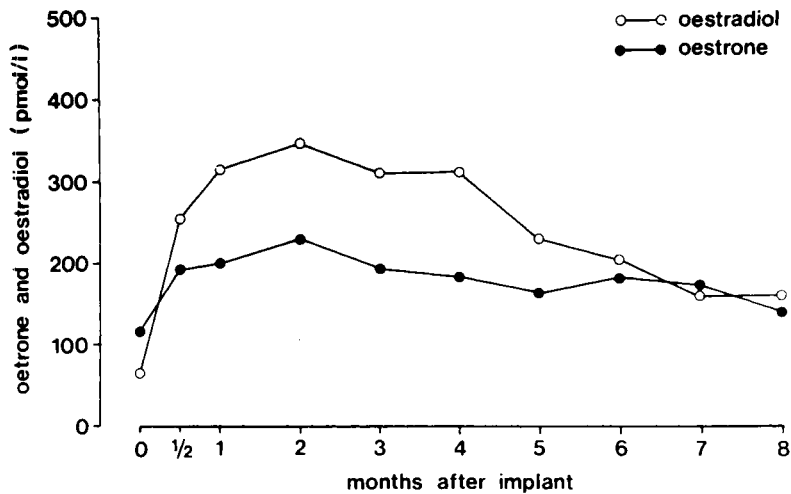


FIG. 3

The mean concentrations of oestrone and oestradiol in peripheral plasma following an implant of oestradiol (50 mg).

plasma FSH and LH. The concentration of plasma testosterone was not altered (Table III). The concentration of oestradiol was maximal at two months, reaching a level of 346.7 pmol/l. The concentration of oestrone was then at a maximum of 233.9 pmol/l (Fig. 3). The concentration of oestrone started to decrease at four months, but did not return to normal until eight months. The mean ratio of plasma oestrone to

oestradiol changed from a pretreatment value of 2:1 to 1:2.

*Oestradiol (50 mg) plus testosterone (100 mg) implant*

The mixed oestrogen/androgen implant had the same effect on plasma FSH as the oestradiol 50 mg implant (Fig. 2). The concentration of LH was also suppressed (Table IV). The concentration

TABLE III

The concentrations (mean and range) of various hormones in peripheral plasma before and after an implant of oestradiol (50 mg)

Time (months)	FSH* (U/l)	LH* (U/l)	Testosterone† (nmol/l)	Oestrone† (pmol/l)	Oestradiol† (pmol/l)
Before implant	68.6 (42.4-122.0)	46.0 (35.8-65.9)	1.6 (1.4-2.1)	117.4 (61.0-148.1)	67.6 (26.9-97.2)
0.5	15.7 (8.3-26.7)	26.6 (16.9-43.6)	1.4 (1.1-2.0)	197.1 (79.0-260.0)	256.8 (161.6-431.2)
1	21.9 (7.1-32.4)	23.1 (12.0-32.7)	1.9 (1.1-3.1)	200.1 (148.0-272.0)	316.4 (212.4-495.8)
2	28.2 (10.7-32.1)	25.1 (14.4-36.9)	2.1 (0.8-3.7)	233.9 (185.0-303.0)	346.7 (185.4-938.1)
3	29.1 (14.8-43.5)	19.4 (7.8-32.4)	1.7 (1.1-2.6)	195.9 (148.2-260.0)	311.0 (149.6-699.4)
4	24.8 (12.9-40.6)	28.4 (21.0-40.2)	1.8 (1.4-2.3)	188.5 (170.0-210.2)	310.8 (202.0-670.8)
5	31.5 (15.9-51.2)	31.8 (19.9-41.0)	1.6 (1.4-1.8)	165.9 (102.4-267.0)	230.3 (141.0-320.8)
6	57.6 (32.5-82.9)	43.3 (38.7-59.1)	1.7 (1.3-2.1)	188.4 (142.0-240.0)	205.3 (176.2-252.0)
7	54.4 (28.3-80.2)	48.4 (32.6-64.6)	1.5 (0.9-2.6)	172.5 (107.1-214.1)	160.8 (115.9-205.9)
8	66.9 (36.7-120.2)	58.3 (38.7-70.4)	1.2 (0.8-2.1)	143.0 (92.6-196.3)	160.4 (94.3-201.2)

\* Arithmetic mean.

† Geometric mean.

TABLE IV

The concentrations (mean and range) of various hormones in peripheral plasma before and after an implant of oestradiol (50 mg) and testosterone (100 mg)

Time (months)	FSH* (U/l)	LH* (U/l)	Testosterone† (nmol/l)	Oestrone† (pmol/l)	Oestradiol† (pmol/l)
Before implant	67.3 (26.3-130.0)	39.5 (18.8-54.9)	1.0 (0.9-2.8)	68.3 (21.2-81.3)	25.5 (13.7-40.0)
0.5	19.7 (8.6-27.9)	41.4 (18.8-69.8)	4.3 (2.1-6.0)	201.2 (132.4-376.3)	171.8 (57.6-308.2)
1	13.2 (5.8-21.5)	31.9 (1.3-50.6)	5.0 (3.1-6.8)	312.6 (190.2-414.1)	254.6 (120.3-321.4)
2	18.0 (7.9-23.6)	27.1 (11.2-49.9)	3.5 (2.0-4.8)	308.2 (172.4-572.4)	211.9 (121.4-353.6)
3	26.9 (12.4-45.0)	25.3 (15.6-41.1)	3.1 (1.7-5.2)	242.0 (146.1-411.2)	185.0 (108.3-316.0)
4	23.3 (8.2-30.5)	33.4 (11.2-53.8)	3.2 (1.5-4.7)	274.2 (130.1-390.3)	182.9 (112.4-258.6)
5	30.0 (11.2-43.5)	29.7 (9.0-39.2)	1.6 (1.2-2.7)	201.6 (182.2-284.3)	163.7 (109.6-231.9)
6	38.8 (28.1-49.0)	36.0 (19.2-49.2)	1.4 (0.9-2.2)	147.2 (56.8-218.3)	93.6 (51.2-148.2)
7	48.3 (35.3-57.2)	33.9 (29.0-49.3)	—	—	—
8	67.1 (50.4-92.4)	40.2 (29.2-57.3)	—	—	—

\* Arithmetic mean.

† Geometric mean.

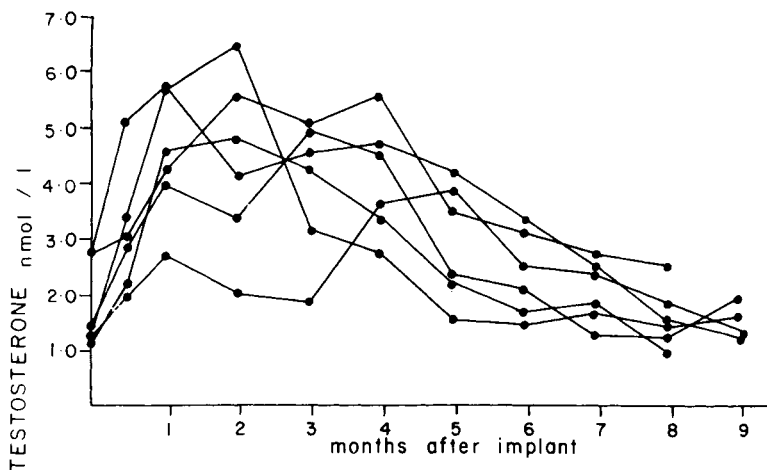


FIG. 4

The concentrations of testosterone in peripheral plasma from patients with an implant of testosterone (100 mg) and oestradiol (50 mg).

of plasma testosterone was raised to 5 nmol/l at one month after implantation, (Fig. 4); the peak concentration at two months coincided with the subjective improvement in libido and the levels returned to normal at eight months.

The concentrations of oestrone and oestradiol were raised as in the patients receiving implants containing 50 mg of oestradiol.

#### Testosterone (200 mg) implant

The administration of 200 mg of testosterone had minimal effect on the concentration of plasma FSH and did not effectively relieve the vasomotor symptoms. The concentrations of plasma testosterone, however, rose to 6.1 nmol/l and reached a peak at six weeks. Pretreatment values were recorded at eight months. There was little effect on the concentration of plasma oestrone or oestradiol (Table V).

#### DISCUSSION

The principal oestrogen secreted during reproductive life is oestradiol-17 $\beta$  from the developing ovarian follicle and corpus luteum. In the postmenopausal patient, oestrone is the major oestrogen produced, and the concentration in the peripheral circulation depends less on ovarian activity with levels remaining fairly constant even in castrated patients (Vermeulen, 1976). It has been shown (Longcope, 1971; Siiteri, 1975) that the main source of oestrone in

postmenopausal women was the peripheral conversion of androstenedione. Adipose tissue has been shown to play an important role in the conversion of androstenedione to oestrone and the amount converted is positively correlated with the weight of the individual (MacDonald *et al*, 1967).

The concentration of plasma oestrogens after ingestion of any preparation show the values for oestrone to have the steepest rise; most interest has therefore been directed towards this hormone and it has been postulated to be the oestrogen associated with endometrial neoplasia (MacDonald and Siiteri, 1974). However, oestradiol is converted to oestrone in the gut (Ryan and Engel, 1953) and it has been shown (Jacobs *et al*, 1977) that both piperazine oestrone sulphate (Abbott Laboratories Ltd) and oestradiol valerate (Schering Chemicals Ltd) produced a striking increase in plasma oestrone, but only a minor change in oestradiol concentration. The ratio of plasma oestrone and oestradiol concentrations rose during therapy with both compounds from a pretreatment value of about 2:1 to 5 to 8:1. Our results showed that with either the 50 mg or 100 mg oestradiol pellet the ratio changed from a pretreatment figure of 2:1 to the more physiological value of 1:2.

In fact, oestradiol is the most potent oestrogen and in order to substantially raise these levels the gut must be bypassed. The administration of

TABLE V

The concentrations (mean and range) of various hormones in peripheral plasma before and after an implant of testosterone (200 mg)

Time (months)	FSH* (U/l)	LH* (U/l)	Testosterone† (nmol/l)	Oestrone† (pmol/l)	Oestradiol† (pmol/l)
Before implant	53.8 (31.6-99.4)	56.2 (34.1-78.9)	2.3 (1.5-3.2)	120.3 (88.2-185.1)	59.8 (46.3-80.2)
0.5	61.4 (42.3-82.5)	47.9 (32.2-62.2)	6.7 (5.2-11.4)	156.6 (91.0-223.2)	92.8 (59.9-139.0)
1	64.8 (29.0-120.0)	40.7 (26.4-57.7)	6.1 (4.9-8.2)	145.2 (113.9-202.2)	96.0 (57.7-214.2)
2	60.7 (20.0-100.0)	33.9 (16.0-48.6)	5.0 (3.3-6.3)	129.7 (53.3-271.4)	106.1 (64.5-236.8)
3	49.6 (32.0-120.0)	34.1 (25.5-47.2)	4.7 (3.8-5.9)	133.1 (53.3-204.2)	120.0 (92.9-158.2)
4	53.4 (29.4-110.0)	39.6 (27.4-52.8)	4.3 (3.8-5.7)	153.9 (112.3-209.6)	98.7 (58.9-139.0)
5	53.2 (33.0-104.6)	32.4 (14.1-52.1)	3.9 (1.9-5.2)	92.7 (64.0-132.4)	73.8 (50.1-89.1)
6	61.9 (41.2-106.1)	58.7 (29.1-89.2)	3.0 (1.1-4.1)	101.1 (71.9-142.3)	69.0 (38.7-101.2)

\* Arithmetic mean.

† Geometric mean.

oestrogens via the vaginal route by means of oestrogen cream has been shown (Whitehead *et al*, 1978a) to cause higher mean concentrations of oestradiol (834.6 pmol/l) than oral therapy with 1.25 mg of Premarin (264.7 pmol/l) (Whitehead *et al*, 1978b), whereas oestrone concentrations were similar (1018.5 pmol/l versus 859.8 pmol/l). Our study has shown that the oestrone and oestradiol levels reached after implantation with 50 mg oestradiol are in fact lower, maxima of 233.9 pmol/l and 346.7 pmol/l at two months. Since the object of safe chemical treatment of any condition is to render the patient symptomless with the lowest possible dose, implantation of oestradiol should prove safer than oral therapy. We have also found the 50 mg oestradiol pellet adequate for the relief of symptoms in most patients and rarely use the higher dose now. Levels of oestradiol with either dose of implant begin to decrease slightly at four months, and this change is noticed by many women who feel that the implant has worn off, suggesting that much of the symptomatology of the climacteric is due to the change in hormone concentrations rather than the low absolute levels.

The pituitary gonadotrophins FSH and LH fall to normal values within two weeks of implanting pellets of oestradiol. Testosterone

implantation of 200 mg has no effect. If the 100 mg pellet of oestradiol is used then the levels of FSH remain impressively suppressed for up to nine months, whereas the 50 mg pellet keeps the levels low for 6-7 months. The concentration of testosterone hardly varies after implantation of 100 mg oestradiol although oestrogen administration may cause an elevation in the plasma concentrations of sex hormone binding globulin and the amount of bound testosterone may therefore be increased (Chakravarti *et al*, 1979), although free testosterone levels will not alter. Implantation with 200 mg testosterone caused an elevation of plasma concentrations to 6.1 nmol/l at two months and 100 mg testosterone and 50 mg oestradiol in combination caused a rise to 5.0 nmol/l. These peak elevations are found by the eighth week, by which time symptomatic improvement in libido has been experienced (Thom and Studd, 1978). But symptomatic improvement is not greater with the testosterone (200 mg) pellet than with the smaller dose, so we always use testosterone (100 mg).

Subcutaneous hormone implantation has been shown to be valuable in treating symptoms of the climacteric, especially loss of libido (Studd *et al*, 1977a and b) and this paper describes the plasma hormone profiles following pellet implantation. These changes differ considerably from those

found after oral administration of oestrone or oestradiol in acceptable doses and further work is in progress to determine whether pellet implantation has any therapeutic advantage over oral oestrogens.

#### ACKNOWLEDGEMENTS

This work was supported by King's Voluntary Research Trust and Organon Laboratories Ltd.

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Received June 25, 1980/Accepted October 20, 1980.