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in evidence, relatively greatest in hyperemesis gravidarum, eclampsia, placenta previa, accidental hemorrhage and ectopic pregnancy. The saving of life in the last 10 yars, even in the last 5 years, by the diminution of puerperal sepsis mortality, however, outweighs the collective improvement attributable to these other causes of death.

Quinquennial Rates fof Maternal Mortality in Scotland, 1931-45

Per 100,000 Live Births by Causes of Death

(From McKinlay,—but order in which causes of death are listed has been changed in order to group together the various septic, toxemic and hemorrhagic causes.)

	RATE PER 100,000		
	1931-5	1936-40	1941-5
Puerperal sepsis	215	120	71
Post abortive sepsis	37	34	33
Phlegmasia alba dolens, embolism	36	38	34
Albuminuria and convulsions	85	76	61
Uncontrollable vomiting	27	23	7
Other toxemias of pregnancy	21	19	15
Placenta previa	29	20	12
Accidental hemorrhage	24	21	14
Other puerperal hemorrhage	40	41	39
Abortion, nonseptic	14	16	12
Ectopic pregnancy	13	10	6
Other accidents of pregnancy	6	3	5
Other accidents of childbirth	54	57	57
Other and unspecified conditions	11	6	7
All causes	613	483	377
All causes less sepsis (+ postabortive sepsis)	361	329	274

Gynecology

MALE HORMONE IN GYNAECOLOGY AND OBSTETRICS AND IN CANCER OF THE FEMALE BREAST*

By ALFRED A. LOESER, M.D.

London, England

PART 1

Introduction

In 1937 the author of this review, and at about the same time a number of French gynecologists, (1, 2, 3) attempted to introduce the use of the male sex hormone into gynecological therapy, having previously demonstrated its chief effects on the human endometrium and the anterior pituitary (4). A decade

* The Collective Reviews published in the Survey represent the views of those invited to present them, and not necessarily those of the Editors.

of clinical experience with testosterone in gynecology, with reports from many authors throughout the world, has elapsed since then.

But when the writer reported his results to the International Congress of Gynaecology at Amsterdam (5) in May, 1938, with the encouragement of the late Professor Laqueur, who was the first to isolate testosterone (1935), no one seemed inclined to inject male hormone into the female body.

Even today many gynaecologists, for instance Hamblen, refuse to use the male hormone in gynaecology, although in the beginning of his own investigations in 1937 (6), Hamblen thought it could be useful in menstrual disorders.

Is the male hormone really hostile to the female body? There is not the slightest doubt that male hormone is excreted in the urine of normally menstruating and pregnant women, as Womack and Koch (7) demonstrated in 1932. The source of these androgens in the female body is the bisexual gland, the adrenal cortex, though the ovary itself may produce some male hormone-like principles. The androgens found in the female urine are not mere degradation products of estrogens.

Only very small quantities of androgens can be found in the urine during infancy. During the reproductive life of women about 42–58 international units are excreted in the urine daily. Men excrete 63–68 international units, and after the menopause 70 and more international units can be found in the female urine daily. The international unit is equivalent to 0.0001 gram of crystalline androsterone and 1 mg. testosterone propionate is equivalent to 50 international units. The daily excretions of androsterone in the female urine fluctuate; brunettes excrete more than blondes, but all of them, from the cradle to the grave, excrete androgens irrespective of their age, complexion and race.

After all, one cannot say that male hormone is foreign to the female body, but is it not hostile to the female organism if artificially administered?

Male hormone sometimes shows gynaecogenic properties and can be synergistic to the twin hormones, oestradiol and progesterone, the products of the corpus luteum. But in the usually administered doses, as well as in massive doses, it counteracts the twin hormones and shows only antigynaecognic effects.

In the natural state, however, the female and male hormones circulating in the blood exist in a relatively fixed physiological ratio. This ratio is by no means definable. Although we have a method of determining the blood estrogens we have no reliable method for the determination of blood androgens. McCullogh and Osborn and more recently Törnblom have described methods for blood androgen determination. Neither is exact. Törnblom was the first to determine blood androgens in women. The variations in women between 20–29 years seem so great (between 0.4 and 33.8 per 100 cc. of blood) that this method cannot be regarded as a reliable one (82).

But this very ratio of the female and male hormone in the blood and tissues determines the sex characteristics; the texture of the skin, the distribution of hair, the tone of the muscles, the timbre of the voice, the bony structure, the play of the capillaries in the endometrium with the resulting quantity of menstrual flow

and the reaction of breast tissue, and also the female character, psyche and sexual behaviour—in short, the whole make-up of the female body, the eternal feminine.

As long as we do not know and determine this ratio, our therapeutic venture with male hormone remains empirical. From animal experiments no cogent conclusions can be derived, as different species react differently to male hormone.

In the following survey no animal experiments will be quoted, and it should be pardoned if not every one of the authors who have published papers about testosterone during the last ten years is mentioned. Those who stood godfathers to the clinical birth of testosterone in gynaecology are not omitted.

PART 2

Mode of Action

The effect of testosterone propionate on the human endometrium was discovered by the author of this article by chance during the treatment of a patient with chronic mastitis (4). It was, so far as the writer can say, the first systematically examined case, as at that time (April, 1937) no publication concerning the action of testosterone on the human breast or endometrium existed.

The writer quotes here his first clinical investigation from April, 1937 as the first fundamental experience on which all the others were built (4).

Miss B. consulted me because of a lump in the left breast, on March 21, 1937. Her genitals were normal, she had always had normal, regular menstruations, her cycle was 3/28. My diagnosis was chronic mastitis; testosterone propionate treatment was commenced.

Last period	17th March	
180 mg. test. prop.		
Last injection	11th April	41 days.
Missed next period		
Diagnostic curettage	27th April	
		Premenstrual endometrium.
		Lump in breast regressing.
Next period	4th May	
600 mg. test. prop.		
Last injection	30th May	57 days.
Missed period		
Diagnostic curettage	30th June	
		Atrophic endometrium.
		Lump disappeared.
Next period	23rd August	
Biopsy	23rd August	
		Normal endometrium in secretory phase.

The patient showed no untoward symptoms during or after the treatment. She continued to have normal menstruations. She married in July, 1939, had her first baby girl (5 lbs.) in March, 1943. She fed the baby for 10 months. I delivered her of her second baby, a boy (nearly 8 lbs.), by means of a Caesarean section in March, 1946. She fed this baby for 6 months. The last examination took place in December, 1947, 10 years after the therapy. The periods remained normal and regular, and no lump has re-appeared in the breast.

From this and later clinical experiments and investigations of Foss (8) it became evident that in normal women:

(1) Testosterone propionate in monthly doses of 100–200 mgs. slowed down the tempo of the normal cyclic development of the endometrium.
(2) Testosterone propionate in monthly doses of 600 mgs. and more arrested the cyclic normal development of the endometrium and rendered it atrophic without exception.
(3) Discontinuation of testosterone propionate administration resulted in normal redevelopment of the endometrium and normal menstrual cycles after a certain time.

There are flowing transitions from the slowing down of the normal endometrial development to the complete inhibition of its growth according to the dosage employed. (The same phenomena in the endometrium are brought about by hypothalamic storms—fear, fright, tension, etc., acting via vegetative nervous pathways directly on the pituitary and the adrenals.)

How can the action of testosterone propionate be explained?

Although the exact mode of action is largely problematical, it could act in any of the following ways:

(a) centrally on the hypothalamic-pituitary release mechanism of the gonadotropes (anti-gonadotropic).
(b) by inhibiting the formation of the follicle or corpus luteum in the ovary (anti-ovarian).
(c) by counteracting the blood and tissue estrogens directly (anti-estrogenic).
(d) by local action on the myo-endometrium (anti-haemorrhagic).

Many authors (1, 4, 6, 8, 9, 11–14) found that gonadotropes in the urine of women who were treated with large or massive doses of testosterone propionate disappear partly or completely from the urine. It is true also at the menopause when as a rule great amounts of gonadotropes are excreted in the urine.

Testosterone therefore acts on the release mechanism in the hypothalamic–anterior pituitary system. Either the production in the anterior lobe of the pituitary may be inhibited or the stored gonadotropic hormone is not released. We do not know the mode of action in the human being. Massive doses of testosterone inhibit also the release of thyrotropic hormone from the anterior pituitary (10), and the release of lactogenic hormone after childbirth (15–17). The male hormone as well as the female hormone may act not only on the different cells in the anterior pituitary. It may act on a higher level, in the hypothalamus, the head ganglion of the vegetative nervous system from which sympathetic and parasympathetic nerve fibres innervate the pituitary gland. The pituitary is under the control of the hypothalamus, the centre for emotional response.

Male hormone in large doses is anti-gonadotropic

Whatever the central mechanism, the effect on the ovary is rapid. The ripening of the follicle in the ovary and the formation of the corpus luteum is slowed down, postponed or completely stopped. Male hormone administration has therefore an indirect inhibiting action on the ovary and slows down or completely inhibits the production of estrogens and progesterone. Greenblatt (18) im-

planted tablets of 400 mgs. of testosterone and for various indications performed laparotomy a few months after the implantation. He found fresh corpora lutea. But if greater quantities of male hormone are administered and the laparotomy is performed immediately after the cessation of male hormone therapy no fresh corpus luteum is found.

Testosterone in large doses is anti-ovarian

Does a certain quantity of male hormone neutralize a certain quantity of female hormone, as acid neutralizes alkali in a test tube?

The shrinking non-estrogenic vaginal epithelium of a menopausal woman shows cornification and glycogen deposition in the vaginal cells after treatment with a certain amount of estrogen, as if the menopausal woman had returned to her reproductive span of life. As soon as a certain amount of testosterone propionate simultaneously is injected, the rejuvenating effect of the estrogen is nullified, and the menopausal vaginal epithelium remains menopausal (19, 20). 25 mg. testosterone neutralizes 0.5 mg. oestradiol (19). The ratio is 50:1. This neutralizing ratio is not the same for the endometrium. Here, according to Ferin (21, 22) 600 mg. testosterone neutralizes 16 mg. stilboestrol. This ratio is 30:1. Assuming a monthly production in the normal woman of 15–20 mg. oestradiol—there is a wide range in different individuals—the requisite neutralizing dose of testosterone would be 600 mg. The ratio would again be about 30:1. This dose of 600 mg. testosterone which renders a normal endometrium atrophic was previously called by the writer the hormonal atrophying dosage (H.A.D.) for the endometrium, and may be taken as a standard dosage, which must either be decreased or increased according to the desired clinical effect.

The male hormone in large doses is anti-estrogenic

Though moderate doses (150–200 mg.) of testosterone reduce the loss of blood in hypermenorrhoea, they have little effect on the endometrium, which may remain in the same condition as it was before the administration of the male hormone. If it is estrogenic before the treatment it may remain estrogenic afterwards. If it is in the secretory phase it may remain so afterwards, but in all these cases the loss of blood during the following period is reduced to a normal one, or in a normal one, to subnormal.

Testosterone has a specific contractile effect on the myometrium (23) in the blood-vessel occlusion. But, as will be seen in an article to be published by the writer in the near future in the Journal of Obstetrics and Gynaecology of the British Empire, the action is more probably on the endometrial vascular bed itself (81). If testosterone propionate (125 mg. or more) dissolved in propylene glycol is injected intravenously, the vessels of the endometrium in a majority of cases constrict after a short temporary vasodilatation.

The same phenomenon can be observed more directly in laparotomy, when the uterus is seen to blanch 2 minutes after the injection and to remain blanched for a further 2 or 3 minutes. It is reasonable, therefore, to assume that more prolonged dosage may produce a similar and more permanent effect.

Testosterone in large doses is therefore anti-haemorrhagic

As we have seen, androgens may have 4 different modes of action. It is not known which of them is the most important or whether one or more actions are synchronized.

Whichever it may be, the question asked in the beginning of this article, whether the male hormone is hostile to the female organism, must be answered in the affirmative without even taking into consideration the unpleasant masculinizing effects androgens can produce in the female body, with which the writer will deal later on.

In spite of this one cannot overlook the fact that androgens act as an antidote if too many estrogenic principles are produced and circulate in the female body, and in logical consequence one should use androgens in real hyperestrogenic conditions. One should not forget also that a surplus of estrogens is hostile to the female body.

As in the vegetative nervous system parasympaticus and sympaticus must be in balance, so in the primitive nervous system—that is the entity of the endocrines—the estrogens and cholinergic-like principles, if the writer may appropriate Dale's expression, must be in balance with androgens, the adrenergic-like principles in the female body.

Estrogens are the steadily, discreetly working principles. They have the upper hand over the androgens under normal conditions. But if they are in excess, they should be counteracted by androgenic principles in order to maintain the endocrine female/male ratio. *For this purpose and for this purpose alone the male hormone should be used in gynaecology.*

With this in mind we have to discuss the clinical application of the male hormone.

PART 3

(a) *Hypermenorrhoea: Menorrhagia, Metrorrhagia*

Numerous authors (4, 8, 11–14, 24–35) have employed male hormone for this condition. Some use small doses of 5–10 mgs. 3 or 4 times during the second half of the cycle for hypermenorrhoea; others begin the therapy in the first half of the cycle. Testosterone therapy should always be started before the follicle ripens or a corpus luteum is formed; the result is more reliable and smaller doses can be used than later when the follicle is already matured.

In cases of menorrhagia and metrorrhagia larger doses of testosterone propionate are necessary. A dosage of 200–300 mgs. monthly in intramuscular injections is advisable, to be commenced just when menstruation is finished, but in cases of severe meno-metrorrhagia up to 400 mgs. can be given. If sublingual tablets are preferred (and this should be the therapy of choice) usually at least 300 mg. up to 500 mgs. can be recommended. Five hundred monthly mgs. of oral testosterone can be administered with impunity in severe cases, especially where there are multiple small fibromyomata. The flooding in these conditions can be well controlled in this way. If one requires a quick result, 4 injections of 25 mgs., each during the first fortnight of the cycle, may be combined with 10

mgs. oral testosterone daily for 20 days. This sequence should be repeated 2 or 3 times to regulate subsequent menstruations. In the majority of cases, if there are no submucous fibroids, the patient will benefit for a considerable length of time, and often for years.

One or 2 days after the beginning of androgen therapy there is occasionally some irregular loss of blood due to temporary dilatation of the endometrial vessels, before they constrict. Recently a method of administering testosterone and progesterone in combination has been recommended (36); testosterone because of its haemostatic properties and progesterone to induce desquamation of the hyperplastic or malfunctioning endometrium. The bleeding is said to be arrested on the first or second day after treatment has been commenced. The technique is to give 25 mgs. of testosterone and 10 mgs. of progesterone on 5 consecutive days.

(b) *Fibroids of the Uterus*

Patients with multiple fibroids are frequently relieved by the administration of male hormone. The menorrhagia and dysmenorrhoea are alleviated and the tumour materially reduced in size, small fibroids apparently disappearing. Amounts of 300–400 mgs. of testosterone monthly, intramuscularly, are necessary. The results, however, are usually only transitory and this therapy can be recommended only in patients who are poor risks for major surgery. As preoperative treatment such a procedure is beneficial, especially as these patients regain strength as the blood picture approaches normality. In premenopausal patients suffering from menorrhagia due to small fibroids it is the therapy of choice, as often they can be tided over until the menopause induces normal shrinkage of the fibroids. In this way hysterectomy can often be avoided (37, 38, 39).

(c) *Endometriosis*

In endometriosis massive dosage only will help, between 500 and 1000 mgs. monthly being necessary (40, 41). The disease can be brought to a temporary standstill, but a real cure is unobtainable. Here also male hormone therapy can be regarded as a predominantly pre-operative and perhaps post-operative measure. However, in cases of widespread endometriosis the patients feel very much relieved, so that testosterone administration is the method of choice in many cases, locally as well as generally. On the other hand it should not be forgotten that a monthly dose of 400 mgs. or more can bring about masculinizing effects and *one will not find a woman the world over, who would not prefer her disabling floodings, pain, and, if necessary, a mutilating operation to a beard growing on her chin or upper lip and to a low-pitched male voice.*

The administration of male hormone by subcutaneous implantation is of value in this connection. In 1939 the writer, in the presence of the originator of this method, A. S. Parkes, implanted tablets of testosterone, and was for a long time partial to this method. Longer experience has, however, shown that oral therapy gives as good though perhaps less rapid results. Apart from its simplicity

this method has the advantage of easy control, so that symptoms of masculinization can be arrested at their earliest appearance.

(d) *Menopause*

The menopause is not usually accompanied by hyperestrinemia but sometimes large amounts of estrogen are present at this time as a result of the compensatory action of the anterior pituitary and adrenal cortex. In certain cases androgenic is preferable to estrogenic therapy. Patients who have or have had cancer for example, particularly breast cancer, should never be given estrogens for their menopausal disturbances; androgens are preferable (42). The same holds good for patients with a familial cancer history, and for women in whom small doses of stilboestrol provoke bleeding. In these cases an adequate monthly dose is 100-300 mgs. of testosterone by mouth or 50–100 mgs. by implantation. All the well known vasomotor symptoms of the menopause subside fairly quickly; hot flushes, attacks of sweating, depression, vertigo and anxiety are relieved. But these small doses will not control excessive uterine haemorrhages.

In the great majority of cases the estrogens are superior to androgens in the control of menopausal symptoms; the latter should be reserved for those cases where the former are badly tolerated or provoke untoward symptoms (43, 44, 45, 46).

Estrogens and androgens together have been given to menopausal women and the published results (49, 50) are good. In the writer's experience the optimum combination is a ratio of 10 mgs. methyl testosterone and 1 mg. diethyl stilboestrol, taken every other day. The male hormone not only prevents a possible estrogenic bleeding but acts as a general stimulant on the general condition, so that the fatigue and many of the nervous symptoms disappear.

The normal female/male hormone ratio is disturbed at the menopause and may more easily be restored with this combined therapy. But the first essential in treatment is the abolition of distressing symptoms and this is best accomplished by giving as small doses of hormone as possible for the shortest possible time, the treatment being interrupted from time to time, since the final effects of hormone therapy, so far as stimulation of new growths is concerned, are not yet known.

(e) *Premenstrual Tension*

Major premenstrual molimina disappear most abruptly with the onset of menstruation and may be followed by hypermenorrhoea or hypomenorrhoea. Many of the distressing symptoms are said to be caused by hyperestrinemia, but this is doubtful. Testosterone has been given on this hypothesis by several authors (32, 33, 47) in a dosage of 10–50 mgs. during the second half of the cycle, and in many cases with considerable relief, but all the symptoms of premenstrual tension, oedema, abdominal distension and emotional stress are adequately relieved by Greenhill's ammonium chloride technique (48)—1 gram 3 times daily 10 days before the onset of the menstrual flow. There is no justification for the use of

androgens when estrogens, progesterone, ammonium chloride and similar harmless preparations can be used with equal effect.

(f) *Intracyclic Bleeding*

Mid-menstrual bleeding is mostly the result of transitory hyperestrinemia, and calls for treatment only where the bleeding persists more than a few hours or a day. Oral testosterone in 5 mg. doses given daily throughout the intermenstruum, or 25 mg. hypodermically 4 times in the first half of the cycle, abolished the symptoms without interfering with ovulation (48, 49).

(g) *Dysmenorrhoea*

In dysmenorrhoea, the causes of which are so manifold that they cannot here be enumerated, testosterone therapy seems to have no real place in spite of the good results which have been reported by several authors (51–53) and which the writer has himself seen. The rationale is based on the suggestion that functional dysmenorrhoea occurs only in the presence of a corpus luteum, and that if this is inhibited the period should be rendered painless. But the suggested oral dosage of 20 mgs. given daily for 20 days is not large enough to prevent ripening of the follicle and corpus luteum formation. Whether testosterone in these small doses is able to arrest the peristaltic movements of the uterine and tubal muscles, another cause of functional dysmenorrhoea (54), is more than doubtful.

The difficulty of correct assessment of hormone therapy in these cases is evidenced by the apparently complete and permanent cure in a personal case where normal saline was substituted for the injection of male hormone without the patient's knowledge. In view of the many and varied factors involved and the success attending safer methods, the routine administration of testosterone to these patients would appear not to be justified.

(h) *Mastopathia, chronic mastitis, fibroadenoma*

The ducts and acini of the breast react to the varying hormonal concentrations during the menstrual cycle. Both show marked premenstrual hypertrophy with regression of the ductular epithelium and reduction in the acinar size at menstruation, i.e., when the blood estrogen and progesterone content is at its lowest. If the estrogen blood level is raised, premenstrual mastalgia may result. Hyperestrinemia may bring about chronic mastitis, the breasts presenting nodules or small cysts from the size of a pea to that of a pigeon's egg.

Androgens may be employed to counteract the estrogen surplus in these cases. The effectiveness of androgens may be due to a direct action on the breasts, as local androgen administration in the form of ointments or androgen suspension in alcohol can bring about the desired effects.

It is often striking to observe the promptness with which this therapy will alleviate the symptoms of both true mastopathia and chronic mastitis, the cystic changes of the latter undergoing rapid regression (2, 3, 4, 9, 11, 58). The dosage recommended is 250 mgs. monthly equally distributed throughout the period and repeated once or twice in subsequent cycles, for otherwise relapse is common.

Dosage supervision is necessary, however, for testosterone in this quantity often interferes with ovulation, and masculinization is an ever present danger in spite of the hyperestrinemia which is the basis of all these cases.

(i) *Sterility*

In some cases of sterility with no organic lesion there is secreted in the mid-menstruum an abundant viscid, glary cervical mucus. This discharge is acid and hostile to spermatozoa, which cannot penetrate it. But it can be considerably diminished if testosterone is given in small daily doses, up to a monthly total of 150 mgs., during the first half of the cycle, and resulting conception is by no means infrequent. Excess cervical mucus, in the absence of cervicitis, is usually the expression of a hyperestrinemia. Testosterone would in these cases be the logical counteracting agent (55) and is worthwhile trying.

(j) *Frigidity*

One cannot discuss within the framework of this article the complex question of absolute and relative frigidity. Estrogens and androgens have been given empirically for its relief (56) and there is no doubt that the latter almost universally produces an aphrodisiac reaction when given in large doses (57) (Last comprehensive review 10th Congress Français du Gynécologie, 1946). It acts locally by stimulating enlargement of the clitoris, an effect which may also be produced by the topical application of testosterone ointment, but it may also increase the sexual drive. This increase in libido is, however, purely temporary and the aphrodisiac effect of male hormone should not be a medical indication for its employment, for the dangers of masculinization more than offset any temporary stimulation. The psychic effect is a real one, and can be a source of considerable embarrassment in elderly women undergoing testosterone therapy for some other condition, e.g. breast carcinoma (27).

(k) *Disturbances of Micturition*

The French authors, Mocquot and Moricard, (1) were the first, as far back as 1936, to use male hormone in functional troubles of micturition in women, especially nocturia, with good results. The genito-urinary system is probably under estrogenic influence. We know this from the disturbances which occur during pregnancy and during the menopause, where probably not an estrogen deficit but an estrogen surplus is the cause. Castration cases and menopausal amenorrhoea sometimes show an increased estrogen level, when anterior pituitary and the adrenal cortex are hypercompensating. The male hormone may increase the maximal intravesical pressure, and may act on the kidney itself or on the water balance and the electrolyte metabolism.

In cases where fibroids are associated with frequency of micturition one should attribute the good results after male hormone therapy not only to the action of testosterone on the urinary system itself, but more to the action on the fibroid. Nocturnal frequency can well be alleviated by testosterone doses up to 400 mgs. without fear of arrhenomimetic phenomena (59). Familial enuresis in children can be arrested (60).

PART 4

Other Clinical Indications

(1) *Pelvic Inflammatory Disease.*

Male hormone therapy is of value in chronic pelvic inflammation because of its property of suppressing the menstrual flow and so diminishing congestion. This is particularly true when menorrhagia is a prominent symptom. Doses up to 650 mgs. monthly have been given with good effect (61), but virilism may be an unwelcome accompaniment unless closely supervised. This method would appear to be particularly indicated in tuberculous adnexitis, but there is no record so far of its application to this condition.

(2) *Hyperemesis gravidarum.*

In early pregnancy, by contrast with the later months, women react to moderately small doses of androgens, and good results have been obtained by their administration in cases of hyperemesis (62), particularly when the vomiting is accompanied by a high estrogen blood level.

(3) *Suppression of Lactation.*

Androgens are capable of suppressing lactation in the same way as estrogens, i.e., by their inhibiting action on the release of the lactogenic hormone from the anterior pituitary (9, 15, 16, 17, 63, 64, 65). Treatment must be commenced immediately after delivery, as established lactation remains unaffected, even by extremely high doses (500 mgs.). Some authors have succeeded in preventing lactation with small monthly doses of 100 mg., others used up to 250 mgs.

The advantage of testosterone over estrogen for this purpose is that the former does not delay either myometrial or endometrial involution (66), while estrogen does. Male hormone delays the regeneration of the surface epithelium in the uterus (67). Testosterone also appears to exert a more rapid and complete effect on the painfully engorged breast. Lastly, its symptom withdrawal curve is much less steep, so that a more prolonged effect is obtained and recrudescence of lactation, which is so commonly seen after stilboestrol suppression, is avoided.

It cannot, of course, be too strongly emphasized that the artificial inhibition of lactation is blatantly unphysiological, and should not be undertaken except for the strongest indications. Apart from the obvious general physical and psychological effects of its interruption, quite apart from the adverse influence on the child, there is definite evidence that the practice is locally cancerogenic, particularly where the suppression is incomplete. It is established that cancer of the breast was extremely common in Chinese women of the Mandarin class during the Ming period, who, abhorring large breasts, avoided lactation and handed over the newborn to their wet-nurses, among whom the incidence of breast cancer was very low. The cause of the malignant change probably lies in the artificially continuous hyperestrinemia, since the women had children in quick succession, but whatever its pathological basis, the risk is a very real one.

If lactation *must* be suppressed, male hormone is preferable to stilboestrol for

the reasons given above, and also for the possible cancerogenic effect of the latter, particularly when there is a familial cancer history. There is little danger of virilism, for puerperal women seem curiously resistant to this complication.

(4) *Prematurity.*

The full term infant carries out with it a relatively high concentration of sex hormones, which are correspondingly deficient in the premature child. Male hormone given intramuscularly appears to be remedial, stimulating metabolism and causing a rapid gain in weight (68).

PART 5

General Actions of Male Hormone

(1) *Effects on the blood calcium.*

A single injection of 20 mg. testosterone raises the blood calcium within 2 hours without changing the urinary output of phosphates (69). The reduction in the urinary excretion of inorganic phosphorus, potassium and creatine after testosterone application points to a somatotropic influence of androgens (70). Early epiphyseal closure in young girls who are subjected to androgen treatment could result. Young girls should not be treated with large amounts of androgens.

On the other hand the hormone favours callus formation and calcium deposition after complicated and malunited fractures (71) and has favourable effects in osteoporosis (72). This fact will be discussed later when the gratifying effect of testosterone on the bone metastases of breast cancer is described.

(2) *Effects on the haematopoetic system.*

Testosterone has a stimulating effect on the bone marrow. The number of erythrocytes and haemoglobin are increased, especially in cases in which normocytic and hypochromic anaemia complicate hypopituitarism (72, 73). The blood creatine is similarly raised and the sedimentation rate accelerated in the majority of cases after the fourth month of pregnancy (75).

(3) *Metabolic Effects.*

Testosterone induces nitrogen, sodium and water retention and raises the basal metabolic rate. The retained nitrogen is transformed into protein with resultant increase in body weight.

(4) *Effects on hypopituitarism.*

Testosterone has been used with very good result in the posttraumatic and postpartum haemorrhage syndrome known as Simmonds' disease (74). These cases show loss of sexual function, amenorrhoea, loss of libido, usually sterility, low basal metabolic rate, low excretion levels of follicle-stimulating hormone and extremely low excretion of 17-ketosteroids, apart from the common asthenia. Twenty mg. male hormone given weekly for 20 weeks improves these conditions very much. As mentioned above, the hypochromic anaemia complicating hypo-

gonadism and hypopituitarism is improved and testosterone seems to enable the marrow to utilize haematinic principles and restore the cellularity to normal.

Patients with Cushing's syndrome and Addison's disease react after testosterone in similarly favourable manner.

(5) *General stimulative effect.*

There is a curious side effect which may be noted in most cases undergoing male hormone therapy, an improvement of the blood picture, an appreciable gain in weight and general increase in visceral muscle tone. With this observation as a basis, the author of this article has made it a practice for the last 2 years to give male hormone intramuscularly as a routine in doses of 10–20 mgs. for 7 to 10 days in postoperative hysterectomy (because of fibroids) and post-delivery cases, particularly when undue haemorrhage has been a complication.

PART 6

Methods and Disadvantages of Testosterone Propionate Administration

Testosterone is the most potent of all the androgens. It is prepared commercially from cholesterol. Esters of testosterone, especially that of propionic acid, surpass free testosterone in activity. The propionate is therefore the form commonly employed. The route of administration is usually by intramuscular injection. It can be given also by inunction ointment or in alcoholic solution, especially when a more local effect is desired (i.e., in mastitis), but in this form its action is very weak. As sublingual tablets (methyl testosterone) it can be given by mouth with very good effect.

Testosterone is rapidly absorbed by the gastrointestinal tract and secreted in the urine and feces. There is usually an increase in the urinary androgens after administration of large doses of testosterone.

Ethynyl testosterone (pregneninolene) is less effective but has no anti-gynecogenic nor arrhenomimetic qualities and does not inhibit the activity of the anterior pituitary lobe. It is relatively easily absorbed through the skin.

Pellet and tablet implantation have been widely employed. The absorption rate depends on the size of the implantation (27, 77), propionate tablets losing 0.35 per cent of their weight daily, pure testosterone 1.18 per cent (78).

Crystalline testosterone can be given by intramuscular injection as an aqueous suspension of 20 mg. to the ccm. It has the advantage of being painless (79). Vaginal and rectal suppositories containing 25 mg. of the hormone can be of value.

In the writer's opinion, the route of choice in the great majority of cases is the oral. Whether we deal with estrogens or androgens, neither of which is indifferent, and sometimes harmful, the method of administration must be easily controllable in order not to transgress the borderline where more damage than benefit results. With oral therapy we can stop at any time, and right on time, as soon as we think we may have transgressed this borderline.

Drawbacks of Androgen Therapy

Androgen therapy is a two-edged knife. Many disabling symptoms may be rapidly and often completely relieved, but over-dosage can cause much damage,

reversible damage, it is true, but still very unpleasant. Hypertrichosis, acne, voice changes, enlargement of the clitoris and undesired increase of libido, are fairly easily produced and inevitably provoke secondary psychological symptoms. In the writer's opinion, based on approximately 1500 cases in the literature and also his own cases (80) the maximum permissible monthly dose is 350 mgs. by injection and 600 mgs. by mouth. This should not be transgressed per month, indeed it should be considerably diminished for patients in whom there is already a tendency to hirsutism. The best control over androgen therapy would be the determination of the estrogen-androgen ratio in the blood, but we are still very far from this goal. The determination of urinary estrogens and androgens is unsatisfactory and of little help in the majority of cases. The metabolism of the androgens in the female body is not completely known.

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PART 7

Cancer of the Breast and Androgens

Estrogens are growth hormones and the female breast responds cyclically to their rhythmical release. Mastopathia, chronic mastitis and fibroadenoma are pathological products of an abnormal reaction to this growth hormone. Androgens, although they may contain a growth element themselves, counteract this hyperestrogenic stimulation, as has been described previously. If cancer of the breast is the pathological end-product of an abnormal reaction to hyperestrogenism, and there is a reasonable basis for the hypothesis, there is here a clear indication for androgen therapy.

In 1938 and 1939 the writer published the first articles (1, 2) about androgen therapy in cancer of the breast. Ulrich (3) published one case of breast cancer treated with androgens. While testosterone had no effect on the very advanced primary tumour itself, temporary amelioration of these hopeless cases was undeniable. But further clinical and experimental experience induced the writer to recommend the implantation of large doses of testosterone twice or thrice yearly after total mastectomy as postoperative prophylaxis to prevent recurrences (4, 5). The male hormone therapy must be continued for years, with yearly doses up to 3000 mgs. or more.

This method was checked by Prudente (10) and Adair (14) is going to try the value of this prophylactic method.

Because of the scarcity of testosterone during the war no further cases of breast cancer could be treated here and the writer's series remained small. But in America from 1942–1947 many surgeons took up and developed these ideas. Farrow (7) used testosterone in the treatment of breast cancer and he studied the action on serum calcium and on skeletal metastases from breast cancer. Unfortunately he used only small quantities and had no results. He even saw an unfavourable effect with the doses he administered on skeletal metastases. The small doses of testosterone employed favoured a hypercalcaemia. Fels (8) reported temporary but striking improvements after massive doses, subsidence of pain, disappearance of vomiting and palpable nodules, and for the first time improvement of the radiological picture of the skeletal metastases, a fact which was confirmed by Adair in 1947 (14).

Abel (9) tried the same therapy in malignant disease of uterine carcinoma with striking temporary improvement. The writer saw temporary improvement in inoperable carcinoma of the ovary in 2 cases (42 and 43 years of age), but no improvement in a patient of 65 years.

Prudente (10) reported on 127 patients with operable tumours localized in the breast with or without axillary metastases. Sixty-four were treated with radical mastectomy alone and 63 underwent mastectomy with testosterone propionate treatment postoperatively. The weekly dosage varied from 25–175 mgs. and was continued over years irrespective of whether virilism resulted. The results

in the patients who had received male hormone were definitely better than in those of the other group. Of the former 90.4 per cent survived without recurrence for 3 years or longer as compared with only 46 per cent of the untreated patients. Prudente had the impression in his large series (which the writer gained in his small series years ago) that postoperative testosterone treatment gives very good results.

Herrmann and Adair (12, 13) reported on patients with soft tissue metastases treated with testosterone propionate doses up to 7000 mgs. for 6 or 7 weeks. One of 3 patients showed an appreciable regression of the metastatic soft part tissue, the other 2 did not react. In 3 other patients who received 3000–4000 mgs. the treatment was not effective. The androgen therapy did not influence the radiosensitivity of the carcinoma, but in most instances an increase of weight in the patients was very marked.

Adair (14) treated patients with bone metastases reserving a total of 2400–3000 mgs. testosterone for 8 to 10 weeks. The blood calcium in cases of advanced bone metastases and bone destruction is 10 to 12 and even 17 mgs. per 100 cc. and comes slowly back to normal after calcium is redeposited in the destroyed area. Alkaline phosphate is necessary for bone repair. The normal limit is 3–5 milligrams. During bone repair under testosterone it goes up at times to 15 milligrams. The areas of bone destruction are filled in with dense callus similar to that seen following X-ray therapy. It is according to Adair more efficacious and longer lasting and more practical than X-ray therapy. If testosterone, according to Adair, has a place in the treatment of recurrences after radical mastectomy it is in young women with grade 2 or 3 growth. Testosterone "is not a cure for breast cancer; its effects are very profound and gratifying." Chase (15) also warmly recommends the use of testosterone for breast cancer in certain conditions. McClure and McGraw (16) have treated 15 patients suffering from breast cancer with male hormone. All but 2 patients showed some symptomatic improvement and were temporarily markedly improved. In 2 there was improvement of cutaneous and subcutaneous nodules. The experience of these authors parallels that of Adair. There was very slight improvement of bone metastases in 4 or 5 patients. The doses used were 100 mgs. 3 times a week for 10 weeks.

Explaining the action of male hormone on breast cancer, the starting point could be the hypothesis that the physiological fixed female/male ratio in the blood and tissues is disturbed either in favour of the female or in favour of the male hormone. A surplus of one of these hormones may be the *causa movens* or *causa remota* of cancer development.

The greatest number of women developing breast cancer is found in the 45 year age group at the average time of the onset of the menopause, when the female/male ratio begins to be disturbed. The ovary fails to respond to the stimulation of the gonadotropic hormones, and the hypercompensating mechanism in the anterior pituitary replaces the falling amounts of ovarian estrogens by hyperproduction of new estrogenic principles in the adrenal cortex, so that the estrogen blood level is not necessarily lowered. It may even be raised.

The second highest peak in the development of breast cancer is in the 60 year age group. Is there a new and corresponding disturbance in the female/male hormone ratio at the close of the menopause as there was at its onset and does this change tend to male hormone preponderance? One thing is certain, that the menopausal urine contains a higher quantity of androgens than before. In women over 60 years also, suffering from breast cancer, female hormone rather than male hormone influences the growth, the latter having no effect or sometimes even stimulating effect in this age group.

It is reasonable to suggest therefore, that the preponderant hormone may be an agent, *causa movens* or *causa remota*, favouring the particular malignant change in the appropriate organ. To the author's knowledge the blood estrogen content has not been determined in cases of breast carcinoma and the determination of the blood androgens is a relatively new and uncertain procedure. But one clinical fact is relevant in this connection and that is, that to secure any appreciable effect on breast cancer or its metastases massive doses of male hormone must be administered. The size of this dose may be gauged from the fact that a preponderance of at least 50:1 must be secured for testosterone propionate to counteract the female hormone in conditions where the estrogen level is normal. In hyperestrogenic conditions the ratio difference must be comparatively enormous, an assumption verified by the practical findings described above.

PART 8

Conclusions

Within a decade the application of male hormone therapy to gynaecology and other special branches of medicine has assumed a position of paramount importance. New forms of treatment come and go with bewildering rapidity, but the permanence of the particular one under review remains without question. Its benefits, however, are by no means unalloyed, and it is sometimes difficult to steer between the Scylla of relieving distressing hyperestrogenic conditions, and the Charybdis of masculinization resulting from treatment. But a *via media* can be found. Male hormone therapy can be advised in all forms of hyperestrinemia in adult life. When used in younger women it should be only a very temporary form of therapy and the dosage must be moderate. *Minute doses of male hormone stimulate femininity, moderate doses depress, and massive doses completely antagonize it.*

Androgen therapy in breast cancer cannot up to now be regarded as a cure, but it is certainly helpful for the bone metastases and pain. It remains to be seen whether or not it will have any value as a postoperative prophylactic.

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