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

Quinquennial Rates for Maternal Mortality in Scotland, 1851-54
Per 100,000 Live Births by Causes of Death
(From McKinnlay)—but order in which causes of death are listed has been changed, order to group together the various septic, toxemic and hemorrhagic causes.

<table>
<thead>
<tr>
<th>Cause</th>
<th>1851-5</th>
<th>1852-6</th>
<th>1857-8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puerperal sepsis</td>
<td>215</td>
<td>190</td>
<td>111</td>
</tr>
<tr>
<td>Post abortive sepsis</td>
<td>37</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td>Phlegmasia alba dolens, embolism</td>
<td>36</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td>Albuminuria and convulsions</td>
<td>27</td>
<td>33</td>
<td>5</td>
</tr>
<tr>
<td>Uncontrollable vomiting</td>
<td>27</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Other toxemias of pregnancy</td>
<td>21</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Placenta previa</td>
<td>20</td>
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<td>12</td>
</tr>
<tr>
<td>Accidental hemorrhage</td>
<td>24</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Other puerperal hemorrhage</td>
<td>40</td>
<td>41</td>
<td>10</td>
</tr>
<tr>
<td>Abortion, nonseptic</td>
<td>14</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>18</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Other accidents of pregnancy</td>
<td>6</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Other accidents of childbirth</td>
<td>54</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>Other and unspecified conditions</td>
<td>11</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>All causes</td>
<td>618</td>
<td>613</td>
<td>371</td>
</tr>
</tbody>
</table>

These figures represent a significant reduction in maternal mortality during the 1850s, indicating the improvement in obstetric care and public health measures during that period.
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 Gynecology at Amsterdam (6) in May, 1938, with the encouragement of the gynecology in many countries, no one seemed inclined to inject male hormone into the female body.

Even today many gynecologists, for instance Hamblen, refuse to use male hormone in gynecology, 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 women, but only very small quantities of androgens can be found in the urine of pregnant women, as Woenack and Koch (7) demonstrated in 1932.

The sex hormones of the adrenal cortex, which are testosterone propionate and 1 mg. testosterone propionate, are the most effective hormones found in the female urine. But it is not the androgens that are harmful, since they are not excreted in the urine of normal menstruating women.

To the writer, this raises the question of whether there is a place for male hormone in gynecology. The answer is yes, but it must be used with caution and only under the supervision of a gynecologist. The use of male hormone in gynecology is still in its infancy, and more research is needed to determine the proper dosage and method of administration.

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, as far as the writer can say, the first systematically planned 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 most fundamental experience on which all the others were built (4).

---

<table>
<thead>
<tr>
<th>Period</th>
<th>Date</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>17th March</td>
<td>11th April</td>
<td>41 days</td>
</tr>
<tr>
<td>27th April</td>
<td>4th May</td>
<td>Prenomenstrual endometrium. 67 days</td>
</tr>
<tr>
<td>30th June</td>
<td>23rd August</td>
<td>Atrophic endometrium. 7 days</td>
</tr>
</tbody>
</table>

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Nina B., residing near a lake in the left breast, on March 21, 1937. Her genitalia were normal; she had had normal, regular menstruations, her cycle was 28/28. Her diagnosis was chronic mastitis; testosterone propionate treatment was commenced.

---

The patient showed no untoward symptoms during or after the therapy. She continued to have normal menstruations. She married in July, 1939, had her first baby girl (by forceps), born in March, 1942. She fed the baby for 10 months. I delivered her of her second baby, born (by forceps), 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.
From this and later clinical experiences and investigations of Foss (5) it came evident that in normal women:

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

There are flowing transitions from the slowing down of the normal endometrial development to the complete inhibition of its growth according to the degree of the female hormone 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 can act in any of the following ways:

(a) centrally on the hypothalamic-pituitary release mechanism of the gonadotropine (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 more adequate amounts of gonadotropes are excreted in the urine.

Testosterone therefore acts on the release mechanism in the hypothalamic-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 luteotropic hormone from the anterior pituitary (10), and the release of luteotropic hormone after childbirth (16-17). In male hormone and 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-parsymathetic nerve fibres innervate the pituitary gland. The pituitary gland 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 therefore an indirect inhibiting action on the ovary and slows down or completely inhibits the production of estrogens and progesterone. Greinblatt (18) noted 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 laboratory is performed immediately after the cessation of male hormone therapy no such corpus luteum is found.

Testosterone in large doses is anti-estrogenic.

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

The shrinking non-estrogenic vaginal epithelium of a menopausal woman shows atrophy and glycogen deposition in the vaginal cells after treatment with a certain amount of estrogen, as if the menopausal woman had returned to her productive span of life. As soon as a certain amount of testosterone propionate intravenously is injected, the rejuvenating effect of the estrogen is nullified, and the menopausal vaginal epithelium remains estrogen poor (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) 40 mg. testosterone neutralizes 1 mg. stilboestrol. This ratio is 30:1. Administering a monthly production in the normal women 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 is one 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 increased 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 by hysterecotomy, 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 cases the loss of blood during the following period is reduced to a normal one, in a normal one, to subnormal.

Testosterone has a specific contractile effect on the myometrium (23) in the rod-vessel oedema. But, as will be seen in an article to be published by the author in the near future in the Journal of Obstetrics and Gynaecology of the Obstetrics and Gynaecology of the British Empire, the action is more probably on the endometrial vascular bed (24). If testosterone propionate (125 mg. or more) dissolved in propyl alcohol is injected intravenously, the vessels of the endometrium in a majority of cases contracts after a short temporary vasodilatation.

The same phenomenon can be observed more directly in laparotomy, when the former is seen to blanch 2 minutes after the injection and to remain blanched for another 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 is synchronized. Whichver 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 affirmatively without even taking into consideration the unpleasant masculinizing effects androgens can produce in the female body, with which the writeridelater on.

In spite of this one cannot overlook the fact that androgens act as an anticoagulant and 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 that too much of the surplus of estrogen is hostile to the female body.

As in the vegetative nervous system parasympathetic and sympathetic must be in balance, so in the primitive nervous system—that is the entity of the adrenals—the estrogens and cholinergic-like principles, if the writer may appreciate Dale's expression, must be in balance with androgens, the adrenegonia—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 estri-nale/male ratio. For this purpose and for this purpose alone the male hormone should be used in gynaecology.

With this in mind we will 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 mature.

In cases of menorrhagia and metrorrhagia larger doses of testosterone preparations 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 injections 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

(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 size of the fibroids 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 recommened only in patients who are poor risks for major surgery. As preparative 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, 5, 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, too, male hormone therapy can be used as a primarily 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, even as well as generally. On the other hand it should not be forgotten that monthly dose of 400 mgs. or more can bring about masculinizing effects and will not find a woman the world over, who would not prefer her disabling flooding, endometriosis, if, necessary, a mutilating operation to a beard growing on her chin or a low-pitched male voice.

The administration of male hormone by subcutaneous implantation 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 hyperestrogenemia 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 andropause is preferable to estrogenic therapy. Patients who have or have had cancer should never be given estrogens for the example, particularly breast cancer, should never be given estrogens because of the menopausal disturbances; androgens are preferable (42). The same holds true 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 10-200 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. In these small doses will not control excessive uterine hemorrhages.

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 (44, 45).

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

The normal female/male hormone ratio is disturbed at the menopause so may more easily be restored with this combination of hormones. But the first month of 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. If treatment is interrupted from time to time, since the final effects of hormone therapy, so far as stimulation of new growth 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 hyperestrogenaemia or hypomenorrhoea. Not of the distressing symptoms are said to be caused by hyperestrogenemia, but the diagnosis is usually obvious. 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,橡ema, abdominal distension and emotional stress are adequately relieved by Greenhill's ammonium chloride technique (48)—1 gram 3 times daily in the period before the onset of the menstrual flow. There is no justification for the treatment of premenstrual tension or its symptoms when estrogens, progesterone, ammonium chloride and similar hormone preparations can be used with equal effect.

(f) Intrauterine Bleeding

Mid-menstrual bleeding is mostly the result of transitory hyperestrogenemia, and for treatment only where the bleeding persists more than a few hours or a few days. Oral testosterone in 5 mgs. doses given daily throughout the menstrual cycles are 25 mgs. 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 himself sees. The rationale is based on the suggestion that functional dysmenorrhoea is due only in the presence of a corpus luteum, and that if this is interrupted the period should be rendered painless. But the suggested oral dosage of 10 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 will act to arrest the peristaltic movements of the uterine and tubal muscles, another cause of functional dysmenorrhoea, is more than doubtful. The difficulty of correct assessment of testosterone therapy in these cases is evidenced by the apparently complete and permanent cure in a personal case where estrone alone was substituted for the injection of male hormone without the patient's knowledge. In view of the many and varied factors involved and the cases attending safer methods, the routine administration of testosterone to all patients would appear not to be justified.

(b) 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 hyperplasia with hyperplasia of the ductular epithelium and reduction in the acinar size at menstruation, i.e., when the blood estrogen and progesterone content is at its peak. If the estrogen blood level is raised, premenstrual mastalgia may result. Hyperestrogenemia 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.

Estrogens 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 well as androgen administration in the form of ointments or androgen suspension which 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 in the latter undergoing rapid regression (2, 3, 4, 9, 11, 58). The dosage recommended is 200 mgs. monthly equally distributed throughout the period and divided once or twice in subsequent cycles, for otherwise relapse is common.
Dosage supervision is necessary, however, for testosterone in this quantity does interfere with ovulation, and masculinization is an ever present danger in cases 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 menstrual fluid an abundant viscous, glairy cervical mucus. This discharge is not hostile to spermatogenic, 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 means of infrequent. Excess cervical mucus, in the absence of cervicitis, is usually the expression of a hyperestrinemia. Testosterone would in these cases be a logical counteracting agent (65) and is worthwhile trying.

(ii) Frightfulness
One cannot discuss within the framework of this article the complex questions of absolute and relative frightfulness. Estrogens and androgens have been given empirically for its relief (66) and there is no doubt that the latter almost always produces an aphrodisiac reaction when given in large doses (57). Last but not least is the local application in cases of hyperestrinemia, 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 as it is most potent in the sexual drive, and 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 reason, e.g., breast carcinoma (67).

(k) Disturbances of Micturition
The French authors, Mecaqu and Marzard, (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 deficiency or an estrogen surplus is the cause. Castration cases and menopausal amenorrhea sometimes show an increased estrogen level, while anterior pituitary and in the adrenal cortex are hyperfunctioning. The male hormone may increase maximal intravascular pressure, and may act on the kidney itself or on the renal balance and the electrolyte metabolism.

In cases where fibroids are associated with frequency of micturition one must 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 of the female hormone on the renal system itself.

Nocturnal frequency can well be alleviated by testosterone doses up to 400 mgs. without fear of hemorrhagic phenomena (69). Familial enuresis in children can be arrested (60).

MALE HORMONE IN GYNECOLOGY AND OBSTETRICS

PART 4

Other Clinical Indications

(a) Pyelonephritis

Male hormone therapy is of value in chronic pelvic inflammation because of its potency in suppressing the inflammatory process and so diminishing congestion. This is particularly true when menorrhagia is a prominent symptom. Dosages up to 400 mgs. monthly have been given with good effect (61). But, virilism may be an undesirable accompaniment unless closely supervised. This method would appear to be particularly indicated in tuberculous adenitis, but there is no record of its application to this condition.

(b) Hyperemesis gravidarum

In early pregnancy, by contrast with the later months, when production of 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.

(c) Suppression of Lactation

Androgens are capable of suppressing lactation in the same way as estrogens, 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 if extremely high doses (500 mgs.) are used. Suppression with small monthly doses of 100 mg., others used up to 250 mg.

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 painful engorged breast. Lastly, its symptom withdrawal curve is much steeper, 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 induction 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 their children to the wet-nurses, among whom the incidence of breast cancer was very high. The cause of the malignant change probably lies in the artificially induced hyperestrinemia, since the women had children in quick succession, whatever its pathological basis, the risk is very real one.

If lactation must be suppressed, male hormone is preferable to stilboestrol for
the reasons given above, and also for the possible carcinogenic effect of the latter, particularly when there is a familial cancer history. There is little danger of virilism, but 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. No hormone given intramuscularly appears to be remedial, stimulating instead and causing a rapid gain in weight (69).

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 urinary excretion of inorganic phosphorus, potassium and calcium after testosterone application points to a somatotropic influence of androgens (70). Epiphysical closure in young girls who are subjected to androgen treatment can result. Young girls should not be treated with large amounts of androgen.

On the other hand the hormone favours callus formation and calcification of bone after complicated and malunited fractures (71) and has favourable effects on osteoporosis (72). This fact will be discussed later when the gratifying effect of testosterone on the bone metastases of cases of carcinoma 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 anaemia 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 results in the postpartum haemorrhage syndrome known as Simmonds' disease (74). These cases often lose sexual function, amenorrhoea, loss of libido, usually start with very low basal metabolic rate, low excretion levels of follicle-stimulating hormone, extremely low excretion of 17-ketosteroids, apart from the common symptoms of very much. As mentioned above, the hypochromic anaemia complicating hypopituitarism is very much.

MALE HORMONE IN GYNAECOLOGY AND OBSTETRICS

Medullary and hypopituitarism is improved and testosterone seems to enable the woman 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 stimulatory 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 mg. for 7 to 8 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, are free from testosterone in activity. The propionate is therefore the form commonly employed. The route of administration is usually 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 in 3 months 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.

Ethyl testosterone (pregnenolone) is less effective but has no anti-gonadotropic nor anti-arrhenomimetic qualities and does not inhibit the activity of the anterior pituitary lobe. It is relatively easily absorbed through the skin. Testosterone and testosterone propionate have been widely employed. The absorption rate depends on the size of the implantation (27, 77), propionate tablets losing 65% 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). Oral 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 indifferently 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 safely and often completely relieved, but over-dosage can cause much damage,
reversible damage, it is true, but still very unpleasant. Hypertrichosis, as a
voice change, enlargement of the clitoris and undesired increase of hair, in
fairly easily produced and inevitably provoke secondary psychological symptoms.
In the writer’s opinion, based on approximately 1500 cases in the literature at
the maximum permissible monthly dose is 350 mg per injection and 600 mg by
mouth. This should not be transgressed per med., and should be considerably diminished for patients in whom there is already
induced. The best control over androgen therapy would be a
tendency to hirsutism. The best control over androgen therapy would like in
the ovaries and testes, but we are still very
determination of the estrogen-androgen ratio in the blood, but we are still very
determination of urinary estrogens and androgens is
far from this goal. The determination of urinary estrogens and androgens is
necessary. The metabolism of the androgens in the female body is not completely known.

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Cancer of the Breast and Androgens

Estrogens are growth hormones and the female breast responds cyclically to their rhythmic release. Mastopathy, 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 cases of Paget's disease and on the cases of cancer, the use of androgens in the treatment of the early stages of breast cancer was not without success. But further clinical and experimental experience indicated the use of androgen therapy as an additional treatment, to be recommended in cases of breast cancer with postoperative recurrence, and as substitute for the operation of mastectomy in cases where mastectomy is not possible.

The male hormone therapy must be continued for years, usually for at least 2 years, and yearly does up to 3000 mgs. or more.

This method was checked by Prudence (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 we had a chance to treat more cases of breast cancer with androgens. In the treatment of breast cancer, the first step is the determination of the serum calcium level and the determination of the calcium content of the bone. If the serum calcium is normal, the patient is considered a suitable candidate for the use of testosterone. The next step is the determination of the serum alkaline phosphatase level.

The use of testosterone is contraindicated in cases of advanced bone metastases, especially if the alkaline phosphatase level is high. The use of testosterone is also contraindicated in cases of severe osteoporosis, osteomalacia, and severe osteitis, as well as in cases of advanced bone metastases, especially if the alkaline phosphatase level is high. The use of testosterone is also contraindicated in cases of severe osteoporosis, osteomalacia, and severe osteitis, as well as in cases of advanced bone metastases, especially if the alkaline phosphatase level is high.

Adair (14) treated patients with bone metastases reserving a total of 2400-3000 mgs. of testosterone for 5 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 the patient will show a decrease back to normal after calcium is reabsorbed in the destroyed area. Alkaline phosphatase is necessary for bone repair. The normal limit is 3-5 milliunits. During bone repair under testosterone it goes up to 15 milliunits.

The areas of bone destruction are filled in with dense callus similar to that seen following X-ray therapy. It is remarkable how much faster the healing process is under testosterone 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.

The use of testosterone is contraindicated in cases of advanced bone metastases, especially if the alkaline phosphatase level is high. The use of testosterone is also contraindicated in cases of severe osteoporosis, osteomalacia, and severe osteitis, as well as in cases of advanced bone metastases, especially if the alkaline phosphatase level is high.
OBSTETRICAL AND GYNECOLOGICAL SURVY

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 make hormone preponderance? One thing is certain, that in menopausal urine contains a higher quantity of androgens than before. Androgen therapy can be used in all forms of hyperestrogenic conditions resulting from treatment. But a via media can be found. Male hormone therapy can be advised in all forms of hyperestrogenism and its effects on the Scylla of relieving distressing hyperestrogenic conditions and on the Charybdis of masculinization resulting from treatment. But a via media can be found.

It is reasonable to suggest therefore, that the preponderant hormone may be either an androgen, oestrogen or estrogens, the blood estrogen concentration in the appropriate organ. To the author's knowledge the blood estrogen concentration in the appropriate organ 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 fact in relation to this connection is that in cases of 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 60:1 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


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