

THE SCOPE OF ENDOCRINE TREATMENT IN ENDOMETRIOSIS

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Has endocrine therapy any place in the treatment of endometriosis? The answer to this question is a matter of considerable clinical importance because present-day therapy of this condition is not satisfactory. The elimination of ovarian function by surgery or radiation will cure the disease. This is not the solution, however, because the majority of cases occur between the ages of 30 and 40 years, and a number under the age of 30 years. Conservative surgery may be successful in younger patients, but, owing to the site and extent of the disease or its recurrence after operation, the results of treatment of this nature are in many cases unsatisfactory. Like the normal uterine endometrium, endometriosis is responsive to the ovarian hormones, and indeed cannot exist in their absence. Hormonal therapy, therefore, suggests itself as a rational form of treatment in selected cases. However, the place, if any, for such treatment has not yet been settled.

In an attempt to determine whether endocrine therapy is of value, an investigation was carried out on 120 consecutive cases of endometriosis, 60 of which were treated with hormones. This investigation was prompted by the clinical problem presented by 2 patients who were first seen in 1950:

Case 1

Mrs. R.C., aged 31, married for 3 years, nulliparous, was seen on 17 March 1950. She complained of severe dyspareunia, increasing dysmenorrhoea which necessitated her taking to bed for 2 days each month, and a continual pain in the right iliac fossa. Three years previously endometriomatous cysts were removed from both ovaries by a left salpingo-oophorectomy and a partial resection of the right ovary. Her symptoms improved for 2 months, but then recurred, more severely than before. Examination revealed an anteverted uterus, a tender right ovary, the size of a hen's egg, and tender nodules in the right uterosacral ligament which, on palpation, reproduced a pain identical to the dyspareunia. The endometriosis had obviously recurred. She pleaded for something to be done, even if the treatment had to be radical. Another operation, however, might have necessitated the removal of the rest of her right ovary, and radiotherapy would have been as drastic. Androgen therapy (the details of which are described below) was prescribed. She reported back 10 weeks later to say that she was 'a different person'. The dyspareunia, dysmenorrhoea, and pain had disappeared. The ovary was smaller, though still tender, and the nodules in the uterosacral ligament had also decreased in size. The course of androgens was repeated after a 2 months' interval. She has now been followed up for 9 years and there has been no recurrence.

Case 2

The satisfactory result achieved in Case 1 encouraged the use of a similar course of androgens in another patient with endometriosis, Mrs. H.A.R., aged 34, nulliparous, who complained of pain in the left iliac fossa and dysmenorrhoea of 4 months' duration. A tender fixed ovarian cyst, 2½ inches in diameter, was felt in the left ovary and purple nodules were seen and felt in the rectovaginal septum. Neither this course of androgens, nor a second one, had any effect on her symptoms and signs. A laparotomy was performed and a large endometriomatous cyst was resected from her left ovary and a smaller one from the right.

An exploration of the literature on endocrine therapy in endometriosis revealed a sparseness of papers and the fact that relatively few cases had been reported.^{3,5-7,9,10,15,18} The need for more extensive clinical research was therefore indicated. This investigation was started in an attempt to assess the exact place of hormonal therapy in the present-day

treatment of endometriosis. The 120 cases encountered represent 3% of 4,200 consecutive White gynaecological patients seen during the period. Sixty of the cases were not treated with hormones because (a) associated pathology was present, e.g. fibroids, (b) the diagnosis was not made before operation, (c) the pathology was endometriosis interna (uterine adenomyosis), or (d) the diagnosis was doubtful and it was considered unwise to postpone operation (e.g. there were big ovarian tumours which may have been neoplastic).

THE CHOICE OF HORMONE AND THE DOSAGE

The hormones that may be considered for the treatment of endometriosis are oestrogens, progesterone, or androgens.

1. Oestrogens

In 1948 Karnaky⁷ suggested the use of very large doses of stilboestrol, and reported 25 cases with satisfactory results. He started with ½ mg. of stilboestrol daily, increasing the dose every 4th day until 5 mg. had been given. This dosage was continued until the patient began to bleed, when the amount was increased to 10 mg. every 15 minutes so that the bleeding stopped. Then 15 mg. was given nightly until the patient bled again, at which time 20 mg. was given every 15 minutes until the bleeding stopped once more. The patients were kept amenorrhoeic for 3-6 months—these colossal doses being increased each time they bled, and Karnaky found that to achieve this he had to continue increasing the dose every 2-6 weeks. Thereafter the administration of stilboestrol was gradually discontinued. He was so enthusiastic about this treatment that he predicted that it would in time become one of the most important forms of therapy for endometriosis.

Since then, however, only a few cases treated in this way have been reported,¹⁵ although Cooke³ described 33 cases. Most gynaecologists have been sceptical or afraid to try this form of treatment because (a) non-pregnant women usually become nauseous and vomit on 5 mg. of stilboestrol, let alone the very large doses recommended by Karnaky (stilboestrol was tried in 3 cases in this series but had to be abandoned after a short while because of uncontrollable vomiting), (b) clinical research over long periods of time would be necessary to ascertain the possible carcinogenic effects of such prolonged and massive therapy, (c) small doses would obviously aggravate endometriosis, and (d) Scott¹⁶ found that in a group of monkeys with experimentally produced endometriosis the lesion did not disappear after large doses of oestrogens were given; in fact it became hyperplastic after about 2 years.

2. Progesterone

The use of progesterone in the treatment of endometriosis (with or without oestrogens) is a subject for clinical research, because some cases of endometriosis are thought to be cured by pregnancy^{8,14,16} (i.e. in the relatively few cases where conception occurs). Kistner⁸ recently treated 12 patients with large doses of both oestrogen and the newer, more potent, progesterones for 2-7 months. Of these patients 9 showed

subjective and objective evidence of improvement, but the author admits that no conclusions can yet be drawn regarding the long-term effect of this treatment.

The rationale of treating endometriosis with progesterone is acceptable in cases where the aberrant endometrium is responsive to both oestrogen and progesterone. More often, however, the lesion is of an immature or 'unripe' variety,¹¹ and in such cases the ectopic endometrium does not respond to progesterone. It is unreasonable to expect a cure in these 'unripe' varieties. Two of our cases are at present undergoing a trial treatment with progesterone, and in these cases histological examination of the ectopic endometrium in the premenstrual phase of the cycle showed a proliferative phase, while that of the normal uterine endometrium was secretory in type.

The results of further clinical trials must be awaited before the therapeutic effect of progesterone on endometriosis can be assessed.

3. Androgens

There is still reluctance, and even rather violent opposition, on the part of many practitioners (and patients) to the use of androgen therapy for gynaecological conditions. This attitude probably stems from the time, about 25 years ago, when the use of androgens was first introduced as a form of gynaecological treatment, and when the dosage was purely empirical. We now know, however, that very big doses were administered at that time, with the result that dramatic virilizing effects occurred. The experience of the past 25 years has clearly shown that the therapeutic dose of androgens is but a fraction of what it used to be in the early experimental days. By giving androgens in correct doses, their therapeutic properties can be utilized without the risk, or with the negligible risk of producing virilizing phenomena.^{1,2,4,12} When clinicians were first feeling their way with androgen therapy, very large doses of 500 mg. of testosterone propionate (equivalent to 2,500 mg. of methyl testosterone by mouth) were given monthly. About 20% of cases then developed virilizing phenomena (acne, hirsutism, lowering of the voice pitch, and enlargement of the clitoris). All subsequent reports, however, have shown that if 300-500 mg. of methyl testosterone are given monthly for 2 consecutive months, the risks of any virilizing effects are less than 1% and, if treatment is stopped as soon as such symptoms appear, the symptoms are reversible.^{1,4,12}

In this series the dosage used was the minimal and safe dose of 10 mg. of methyl testosterone daily by mouth for 2 consecutive months. Where the course had to be repeated, an interval of at least one month, and often many months,¹ was allowed between courses. In only 2 of the 60 cases was there the slightest suggestion of virilizing phenomena. One patient complained of a transitory tenderness of the clitoris; the other, during the 5th course (she had the largest number of courses in the series) began to notice a slight decrease in the size of her breasts, minimal hirsutism around the nipples, and slight voice changes. However, all these symptoms disappeared on cessation of the treatment.

ANALYSIS OF THE CASES TREATED WITH ANDROGENS

A. Patients who did not Respond

The response to androgen therapy in the 60 cases treated is shown in Table I. Fifteen cases (25%) did not respond at

TABLE I. RESPONSE TO ANDROGEN THERAPY IN 60 CASES

No response	15 cases (25%)
Temporarily relieved	22 cases (36.6%)
Apparently permanently cured	23 cases (38.4%)

all, and had to undergo surgical treatment or other therapy.

B. Patients who Benefited by Androgen Therapy

The significant fact is that 75% of the cases showed improvement of varying degree up to complete cure, and that some even conceived. These cases may be divided into 4 groups (Table II):

TABLE II. ANALYSIS OF CASES THAT BENEFITED BY ANDROGEN THERAPY

Group	Response	No. of Cases and percentage
1	Temporarily relieved	22 (36.6%)
2	Completely cured of symptoms and signs. Did not conceive when complaining of infertility	7 (11.6%)
3	Completely cured of symptoms and signs. Did not conceive, but did not complain of infertility	7 (11.6%)
4	Completely cured of symptoms and signs and conceived. Complained of infertility	9 (15.2%)
		45 (75%)

Group 1

Twenty-two cases (36.6%) were temporarily relieved, but the condition recurred. In these cases surgical treatment was carried out, or at least advised. In this group also were some patients whose symptoms were kept under control

TABLE III. CASES TEMPORARILY RELIEVED—NO. OF MONTHS OF RELIEF

Months	1	2	3	4	5	6	12	24	36
No. of cases (22)	0	2	7	1	4	5	1	1	1

until the onset of the menopause (Table III).

Of these 2 were cured for 2 months, 7 for 3 months, 1 for 4 months, 4 for 5 months, and 5 for 6 months; 1 case was cured for a year before symptoms recurred, 1 for 2 years and 1 for 3 years. *The usual duration of temporary cure was, therefore, 3-6 months.*

Group 2

Seven cases (11.6%) were completely cured of all symptoms and signs but did not conceive although infertility was one of the complaints. While the results of androgen therapy were successful, the success could not be called perfect because of the failure to cure the infertility. In 6 of these cases all other investigations for infertility were negative—in 1 the husband was infertile. This persistent infertility, however, is a common experience, even when symptoms and signs are cured by surgery.

Group 3

Another group of cases, also 7 in number (11.6%), were, as far as could be ascertained, completely and apparently permanently cured, but they did not subsequently become pregnant. In no case, however, was infertility a complaint.

Group 4

Cases who can be regarded as complete cures; not only did their symptoms and signs disappear but they also became pregnant. There were 9 cases (15.2%) in this group—quite a substantial percentage in a condition which is so difficult to treat. These cases warrant more detailed analysis:

Case 1

Mrs. E.R., aged 24, had undergone a laparotomy on 30 November 1954 when a chocolate cyst the size of an orange was found in each ovary. A right salpingo-oophorectomy was performed as well as a resection of the endometriomatous part of the left ovary. Two years later she consulted me, complaining of infertility of 2 years' duration and pain in the LIF. Examination revealed an enlarged fixed tender left ovary. Phenobarbitone, $\frac{1}{2}$ gr. daily for 2 months, had no effect. She was then given a course of androgen therapy. The pain and swelling of the ovary disappeared and 6 weeks after cessation of the hormonal therapy she was pregnant.

Case 2

Mrs. E.E.L., aged 26, was referred by her family doctor because of her complaint of primary infertility of 4 years' duration and increasing secondary dysmenorrhoea. A year previously he had performed an appendectomy and had noticed endometriomatous nodules in the pelvic peritoneum, in the ovaries and in the uterosacral ligaments. Nothing was done about these lesions at the time of the operation. Examination revealed the nodules and tender adnexa. Sperm-analyses and tests for tubal patency were normal, and graphs recording basal body temperature indicated the occurrence of ovulation and also showed some pyrexia during menstruation. A month after 2 courses of androgens the patient had amenorrhoea due to pregnancy.

Case 3

Mrs. V.R.B., aged 30, complained of primary infertility of 6 years' duration as well as dysmenorrhoea and dyspareunia. All investigations were negative, except that some pyrexia at menstruation was shown on the basal temperature graph, and nodules could be felt in both uterosacral ligaments. These nodules became large and tender during menstruation. The patient was given phenobarbitone, $\frac{1}{2}$ gr. daily by mouth for 2 months. There was no improvement in the dyspareunia or dysmenorrhoea. On 18 March 1957 a course of androgens was started. She reported on 12 June 1957 with amenorrhoea which was shown to be due to pregnancy.

Case 4

Mrs. S.D., aged 38, was investigated for primary infertility of 4 years' duration. Sperm-analyses were normal, her tubes were patent, and temperature recordings showed evidence of ovulation. There was also some pyrexia during menstruation and this raised the suspicion of endometriosis. During an examination under anaesthesia and a curettage to exclude endometrial tuberculosis, the left ovary was found to be enlarged and, in the immediate premenstrual phase of the cycle 2 firm nodules were felt in the left uterosacral ligament. A diagnosis of endometriosis was made and a course of androgens was commenced on 21 January 1957. Two months after this course of treatment she became pregnant.

Case 5

Mrs. L.H., aged 28, was seen on 2 July 1956 because she had been married for 7 years and was unable to conceive. On 24 June 1957 she had had an operation for endometriosis in Johannesburg. The gynaecologist who operated supplied the information that large endometriomata were resected from both ovaries. Endometriosis was also present in the uterosacral ligaments, but was not removed. The basic fertility factors were investigated and found to be normal, but both ovaries as well as both uterosacral ligaments were enlarged. Two courses of androgens were given, the second commencing on 22 October 1956. She missed her period in January 1957, and this proved to be due to a pregnancy.

Case 6

Mrs. J.V., aged 28, was referred for an opinion about her secondary infertility of 3 years' duration because her doctor had found a normal sperm count, satisfactory ovulation and tubal patency. She also complained of dyspareunia and dysmenorrhoea. On examination her left ovary was enlarged to the size of a hen's egg and tender nodules were felt in the left uterosacral ligaments. Phenobarbitone tablets, prescribed for 2 months, had no effect on the symptoms and signs. The patient was then given methyl testosterone, 10 mg. daily by mouth for 2 months. The course was commenced on 3 October 1957, and on 24 January 1958 she reported with amenorrhoea which was subsequently proved to be due to pregnancy.

Case 7

Mrs. M.F., aged 34, complained of secondary infertility for 3 years and pain in the RIF. Six months previously her doctor had operated on her for the pain and found endometriosis in the pelvic peritoneum and in both ovaries. On examination these areas were very tender. On 9 September 1953 she was given a course of androgens and 3 months later became pregnant.

Case 8

Mrs. P.F., aged 26, complained of primary infertility since her marriage 6 years previously. The left ovary was enlarged and nodules were present in the left uterosacral ligament. She also had increasing secondary dysmenorrhoea. Phenobarbitone therapy over a 2 months' period in no way improved the symptoms and signs. Three months after a course of androgen therapy, however, the ovary was no longer palpable, the nodules had disappeared, and she was pregnant.

Case 9

Mrs. B.M., aged 22, was seen on 22 March 1954. In 1951 her right ovary had been removed for a large adherent chocolate cyst and a large portion of the left ovary had also been resected. She now complained of dysmenorrhoea and dyspareunia, pain in the LIF and primary infertility for 18 months. The left ovary was enlarged to the size of a golf ball, and very tender. A course of androgens was given; the ovary decreased in size and the symptoms disappeared, but she did not conceive. She was not seen again until 19 February 1958. She said that she felt well and her symptoms had not recurred, but she was very eager to have a baby. The sperm-analysis, tubal patency and ovulation were investigated and found to be normal, but conception did not occur. She was given 2 courses of androgens with a month's interval between them. On 8 October 1958 she wrote to say that she had amenorrhoea and nausea; she was subsequently seen and found to be pregnant.

DISCUSSION

Response in Relation to the Age of Patient and Type of Lesion

In this series the response to androgen therapy did not appear to depend on the age of the patient. Young patients in the early 20's responded as well or as badly as patients over the age of 40 years. (Of those who responded 16 were 20-30, 18 were 30-40, and 11 were over 40 years of age. Of those who did not respond 5 were under 30, 8 between 30 and 40, and 2 over 40 years of age.)

The site and the extent of the lesion, however, affected the chances of success. The success rate was good when the ovaries were involved with smaller lesions or when the uterosacral ligaments or the pelvic peritoneum was affected. The diagnosis in nearly all of these latter cases was made during a previous operation (as discussed in the following paragraph). On the other hand, in 3 cases endometriosis was present in laparotomy scars and these cases did not show any improvement. In 4 cases the endometriosis was in the rectovaginal septum and these cases were also resistant to endocrine therapy. Eight of the patients had chocolate cysts bigger than 3 inches in diameter and only one of these responded.

How the Diagnosis was Made

It is well known that the diagnosis of endometriosis is sometimes very difficult. Care was taken to be sure that the patient was in fact suffering from endometriosis before considering her a suitable case for the series. This is one of the reasons why half the cases seen were excluded from the investigation. Of those treated with androgens the diagnosis was made during a previous or subsequent operation in 45 cases. In 11 of the remaining 15 the condition was felt or seen in the uterosacral ligaments or rectovaginal septum, and typical symptoms were present. In 4 of the cases the diagnosis was not proved; however, the history was typical

and enlargement of one or both ovaries was felt, and the cases responded to androgens. Clinically, therefore, there was no doubt that endometriosis was present.

The possible effect of psychotherapy on symptoms, and the possible occurrence of spontaneous cure, was considered. In 25 of the patients who responded to androgens, courses of phenobarbitone tablets were given before androgens were administered. In none of these was there any improvement in symptoms and signs during the administration of the placebo (phenobarbitone).

Mode of Action of Androgens in Endometriosis

In this investigation a clinical approach to the problem of endometriosis was made and clinical facts were analysed. How 38.4% of cases are cured and 36.6% temporarily relieved by androgen therapy, is a matter for speculation. The dose used was very small. It has been shown by Salmon¹² that a dose of 300 mg. of methyl testosterone daily by mouth for a month has no effect on menstruation, pituitary gonadotrophic excretion, pregnandiol excretion, ovarian histology, endometrial histology, vaginal cytology, and basal temperature pattern. This work has been confirmed by Geist and Salmon³, and Shorr *et al.*¹⁷ It has, however, also been shown that a small dose of androgens is therapeutically effective in other disorders (e.g. the dysfunctional uterine haemorrhages) by directly opposing the action of the ovarian hormones.

Since the dose used in these cases did not have any effect on the *normal* intra-uterine endometrium, the ectopic endometrium of endometriosis must be much more vulnerable. This is not unreasonable, for such endometrium is in an area where it has no right to be—in the wrong 'soil' and environment.

Indications for Androgen Therapy

This investigation was carried out to determine whether androgen therapy has a place in the treatment of endometriosis. A retrospective analysis of this series shows that the treatment has a small but definite place in selected cases, and the dosage recommended is harmless. Androgen therapy is of value:

1. As a therapeutic test when the diagnosis is in doubt; 75% of patients with endometriosis who are given androgen therapy show a temporary or permanent improvement in symptoms and signs.

2. When the condition has recurred after one or more conservative operations and the patient is too young to consider radical surgery or a radiation menopause; a third of such cases are likely to show permanent, and a further third temporary, improvement.

3. When the lesion is not easily accessible to surgery, e.g. diffuse spread, or its presence in the uterosacral ligaments.

4. When the patient's only complaint is infertility and the lesion is not gross.

5. In certain selected cases, who have had one or more previous operations, to tide the patient over until the menopause sets in when spontaneous cure occurs.

6. In view of the findings in this investigation it would appear that a course of androgens given *as a routine* after conservative operation for endometriosis may help to prevent recurrence in several cases. A course could also be given pre-operatively, not only because this may result in permanent cure, but also because in a substantial percentage of cases

there will be a temporary improvement confirming the diagnosis and possibly rendering surgery less difficult.

SUMMARY AND CONCLUSIONS

1. In an attempt to determine the place of endocrine therapy in the treatment of endometriosis, 120 consecutive cases were analysed, 60 of whom were treated with hormones. This constitutes the largest series of cases described who were treated in this way.

2. Oestrogens, progesterone or androgens can be used. Androgen therapy is considered the most suitable form of treatment today, although progesterone therapy should be investigated more fully.

3. Androgens were used in 60 cases in courses of 10 mg. of methyl testosterone daily by mouth for 2 months. This was found to be a harmless dose. Minimal temporary side-effects occurred in 2 cases, but these phenomena disappeared on cessation of therapy.

4. Of the 60 cases 25% were completely resistant to treatment; 36.6% were temporarily cured of symptoms and signs (for 3-6 months, but occasionally for 1-3 years); 38.4% were completely and apparently permanently cured—and of this group over a third became pregnant, infertility having been one of the major complaints. The patients who became pregnant are described in detail.

5. Response to treatment does not appear to depend on the age of the patient. The site and extent of the lesion, however, did affect the chances of success. Endometriomatous cysts smaller than 3 inches in diameter in the ovaries, and lesions in the pelvic peritoneum and uterosacral ligaments responded well to androgen therapy. On the other hand, endometriosis in the rectovaginal septum and in laparotomy scars, and lesions in the ovary bigger than 3 inches in diameter, are more resistant to treatment.

6. The mode of action of endocrine therapy is discussed.

7. A retrospective analysis of this series shows that androgen therapy can be most helpful and has a small but definite place in selected cases. The dosage recommended is harmless.

This kind of treatment is indicated:

(a) As a therapeutic test when the diagnosis is in doubt.

(b) When the condition has recurred after one or more conservative operations.

(c) When the lesion is not easily accessible to surgery.

(d) When the patient's only complaint is infertility.

(e) In view of the findings in this investigation it would appear that the routine use of androgens to prevent the recurrence of endometriosis after conservative surgery deserves consideration; likewise a course may be of value pre-operatively.

I should like to thank Prof. J. T. Louw for his encouragement and helpful advice.

REFERENCES

1. Bishop, P. M. F. (1951): *Gynaecological Endocrinology*, 2nd ed. p. 18-19. London and Edinburgh: Livingstone.
2. Bourne, A. M. and Williams, L. H. (1958): *Recent Advances in Obstetrics and Gynaecology*, 9th ed. p. 253. London: Churchill.
3. Cooke, W. R. (1956): *Amer. J. Obstet. Gynec.*, 71, 569.
4. Geist, S. H. and Salmon, U. J. (1941): *J. Amer. Med. Assoc.*, 117, 2207.
5. Hirst, J. C. (1943): *Amer. J. Obstet. Gynec.*, 46, 97.
6. *Idem* (1947): *Ibid.*, 53, 483.
7. Karnaky, K. J. (1948): *South Med. J.*, 41, 1109.
8. Kistner, R. W. (1958): *Amer. J. Obstet. Gynec.*, 75, 264.
9. Marshak, R. H. and Friedman, A. I. (1950): *Gastroenterology*, 14, 576.
10. Masse, Traissac and Dax (1947): *Year Book of Obstetrics and Gynecology*, p. 452. Chicago: Year Book Publishers Inc.

11. Novak, E. and Novak, E. R. (1958): *Gynecological and Obstetrical Pathology*, 4th ed. pp. 212, 213, Philadelphia: Saunders.
12. Salmon, V. J. (1950): *Progress in Gynaecology*, 2nd ed. p. 284, London: Heinemann.
13. Salmon, V. J., Walter, R. I. and Geist, S. H. (1938): *Proc. Soc. Exp. Biol. Med.*, **39**, 467.
14. Sampson, J. A. (1924): *Surg. Gynec. Obstet.*, **38**, 287.
15. Schmitz, H. E. and Towne, J. E. (1948): *Amer. J. Obstet. Gynec.*, **55**, 583.
16. Scott, R. B. (1944): *Ibid.*, **47**, 608.
17. Shorr, E., Papanicolaou, G. M. and Stiamel, B. F. (1938): *Proc. Soc. Exp. Biol. Med.*, **38**, 759.
18. Wilson, L. (1940): *Endocrinology*, **27**, 29.