# Oral Substitution Therapy with Benzestrol for Patients with Estrogen Deficiency

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OVARIAN hypofunction with estrogen deficiency is a common clinical problem. At times it is possible to correct this condition by improving the function of the ovary. When it is impossible to increase estrogen production, because of the menopause or some other condition, and undesirable symptoms occur, one of the estrogenic substances is given to the patient for temporary relief. This substance may be administered by injection, a method with obvious disadvantages,[9] or by way of the gastro-intestinal tract.

Three types of substances have been used orally for substitution therapy: the natural estrogens such as ethinyl estradiol[7] and conjugated estrogens-equine;[6] the stilbenes, synthetic drugs with estrogenic properties, diethylstilbestrol dipropionate[5] and hexestrol;[8] and a new substance, benzestrol, unrelated to either the stilbenes or natural estrogens. The latter substance has been given, in this investigation, to 157 patients. The present paper deals with the results of its use.

Benzestrol, originally called 118B and Octofollin, has been found to be an effective form of oral estrogenic therapy for women.[3,4,12,13,14,15,17,18] Also, it has been administered locally in vaginal suppositories[12,13,14] and parenterally in oil with satisfactory results.[11,12] Prior to clinical investigation, Blanchard, Stuart, Tallman and Stebbins studied the response of rats to this new synthetic drug and found that it had desirable estrogenic properties.[1,2,16]

Benzestrol* is 2,4-di (p-hydroxyphenyl) -3-ethyl hexane. It is supplied in tablets of 0.5 mg., 1.0 mg., 2.0 mg. and 5.0 mg. The tablets are scored so that they may be broken into two equal parts. The daily dose can be divided into two, three or four parts and administered two to four times daily. Frequent administration of the tablets produces a more constant supply of hormone in the blood and is, therefore, more effective. This fact has been demonstrated by implanting pellets of hormone in the body. The resultant continuous absorption has been shown to produce a greater effect mg. per mg. than the intermittant absorption from injections of hormone once or twice weekly.[10]

## CLINICAL MATERIAL

There were 56 cases of natural menopause,† 30 cases of artificial menopause, 30 cases of other conditions with symptoms of estrogen deficiency and 41 cases of conditions without estrogen deficiency. The ages of the patients ranged in years as follows: natural menopause, 39 to 59; artificial menopause, 22 to 58; other conditions with symptoms of estrogen deficiency, 14 to 66; and conditions without estrogen deficiency, 17 to 56. Of the patients in the natural menopause or climacteric period, 29 were no longer having menstrual period, but 27 were still having them, 18 regularly and nine irregularly. None of the artificial menopause patients were having menstrual periods. Of the patients with estrogen deficiency due to other causes, 11 were menstruating regularly, eight irregularly and five infrequently, but six were not having periods. Of the patients without symptoms due to estrogen deficiency, 23 were menstruating regularly. five irregularly and four infrequently, but nine were not having periods.

Individuals in the artificial menopause group previously had had the following operations and treatments: hysterectomy, 19 patients; bilateral oophorectomy, 11 patients; unilateral and partial bilateral oophorectomy, seven patients; x-ray therapy to the ovaries, five patients; and intrauterine radium treatment, one patient. In the group of other conditions with symptoms of estrogen deficiency the following diagnoses were made: ovarian deficiency, ten cases; primary and secondary amenorrhea, eight cases; dysmenorrhea, four cases; premenstrual tension, three cases; senile vaginal atrophy, three cases, frigidity, one case; and chronic mastitis, one case.

## RESULTS

A satisfactory result with at least 50 per cent relief of symptoms was obtained in 43 of the 56 patients with natural menopause, or in 76 per cent. Five patients received no benefit, but since they responded to other estrogens, they were included in this group. For further details of the group see Table 1, which also includes the results with six individual patients to show the percentage of relief due to various daily doses.

Twenty-six patients in the artificial menopause group obtained at least 50 per cent relief of symptoms. This was 87 per cent of the number treated. These results are found in Table 2 along with the data on four individual patients.

The estrogen deficiency symptoms in a number of other conditions were decreased by 50 per cent or more in 19 patients with an average daily dose of 7 mg. Less than 50 per cent improvement was obtained in 11 patients with an average daily dose of 6 mg. These figures do not give the per cent of improvement in the conditions themselves, such as amenorrhea, dysmenorrhea, senility, etc., but only show the per cent of relief from the hot flashes (in a few patients), nervousness and other symptoms of estrogen deficiency of which the patients complained and the objective estimate of per cent of improvement in

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*The Benzestrol used in this study was obtained from Schieffelin and Company, New York.

† The word, menopause, throughout this article is used to include the entire climacteric period, and thus its use is not restricted to the time of cessation of menstruation.

TABLE 1.—*Results with Benzestrol in the Natural Menopause*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Per cent relief* | | 100 | 90 | 75 | 50 | 25 | 10 | 0 |
| No. of patients treated | | 21 | 4 | 8 | 10 | 8 | | 5 |
| Average daily dose | | 8 mg. | 9 mg. | 11 mg. | 6 mg. | 6 mg. | | 12 mg. |
| Examples of individual cases with daily dose | Patient #6 | | | 15 mg. | 10 mg. | 5 mg. | | |
| | Patient #24 | 15 mg. | 10 mg. | | 5 mg. | | | |
| | Patient #25 | 15 mg. | | | 10 mg. | 5 mg. | | |
| | Patient #84 | | 10 mg. | | 5 mg. | 3 mg. | 2 mg. | 1 mg. |
| | Patient #133 | | | | 10 mg. | 5 mg. | | |
| | Patient #153 | | | | 5 mg. | | | 2 mg. |

* It is realized that it is impossible to judge the amount of relief by exact percentages, but because of simplicity the following figures are used in Tables 1, 2 and elsewhere instead of their descriptive equivalents:
(1) 100%—patient entirely free of symptoms.
(2) 90%—patient almost entirely free of symptoms.
(3) 75%—more than 50% improvement but not free of symptoms to the extent of those in group (2).
(4) 50%—patient still has about half of her symptoms.
(5) 25%—less than 50% improvement but having definitely more benefit than those in group (6).
(6) 10%—very slight but noticeable improvement.
(7) 0 —no improvement.

infantile uterus and breasts, personality, atrophy of the vaginal mucosa, etc.

When benzestrol was given to patients with poor vaginal cell cornification, vaginal smear tests showed an increase in the amount of glycogen in the cells and greater cornification. Likewise, an increase in vaginal moisture was frequently noticed. The effect of estrogen stimulation was also observed in the breasts as a few of the patients stated that tenderness in the breasts was caused by taking the tablets. Examination at that time showed greater fullness of the breasts and, in the younger women, an increase in breast development.

Six patients with psychoneuroses, one with manic-depressive psychosis and one with migraine headache received an average daily dose of 5 mg. of benzestrol. An average of 50 per cent improvement seemed to have been obtained in these cases, but relief was believed to be either psychological or due to the pharmacodynamic action of the drug, rather than to its estrogenic activity.

Thirty-three patients, most of whom were classed as psychoneurotics and in whom no estrogen deficiency was believed to exist because of the absence of true hot flushes and other symptoms, were treated with benzestrol in varying amounts from 1 mg. to 15 mg. daily, the average daily dose being about 7 mg. In all these patients, nervous symptoms similar to those of estrogenic deficiency were present, and each patient believed that her condition was due to ovarian deficiency. In some cases the patients had "sweats" and it was difficult to be sure that they were not hot flushes. Five of these patients had had hysterectomies. No beneficial result was obtained in this group, which substantiated the clinical diagnosis.

Benzestrol caused some patients during continuous treatment to have changes in menstruation that were considered undesirable. Uterine bleeding was produced in five menopause patients taking 15 mg. daily. Three of these patients had had bilateral oophorectomies. Menstruation became too frequent in one patient who was taking 3 mg. daily, and it decreased in amount in three patients taking daily 2.5 mg., 3 mg. and 5 mg. respectively. A menstrual period was missed when the following daily doses of benzestrol was given to four patients: 2.5 mg., 5 mg., 5 mg. and 10 mg. Dysmenorrhea was caused in one patient who was taking 15 mg. daily. In all, there were 14 undesirable effects, which comprised 11 per cent of the 132 patients with intact uteri.

Other changes were classed as desirable. Menstruation, previously occurring early, started more nearly on time in three patients with an average daily dose of 9 mg. Mid-period spotting stopped while one patient was taking 15 mg. daily.

Eight patients had changes in menstruation that were probably not caused by the tablets.

Incidentally, one patient became pregnant during a course of treatment with 3 mg. daily.

### TOXIC REACTIONS

Undesirable symptoms were caused by benzestrol in 11 patients (7 per cent). Five patients (3 per cent) had gastro-intestinal disturbances, four with nausea and one with loss of appetite. The following symptoms were also troublesome in the same five patients: acid eructations, one patient; "bad taste in the mouth," one patient; general malaise, one patient; and diarrhea, one patient. Three patients (2 per cent) had itching of the skin, two with a rash and one with general malaise. Three patients (2 per cent) became very nervous while taking the tablets. In addition, one of these patients had flushing of the face and one complained of dizziness.

The average daily dose given to the patients who developed toxic reactions was 9 mg. A smaller dose

TABLE 2.—*Results with Benzestrol in the Artificial Menopause*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Per cent relief | | 100 | 90 | 75 | 50 | 25 | 10 | 0 |
| No. of patients treated | | 9 | 3 | 8 | 6 | 1 | 1 | 2 |
| Average daily dose | | 10 mg. | 17 mg. | 10 mg. | 12 mg. | 5 mg. | 2 mg. | 10 mg. |
| Examples of individual cases with daily dose | Patient #42 | 15 mg. | 10 mg. | 6 mg. | | 2 mg. | | 1 mg. |
| | Patient #74 | | 15 mg. | | | 5 mg. | | |
| | Patient #111 | 20 mg. | 15 mg. | | 10 mg. | | 5 mg. | |
| | Patient #156 | 15 mg. | 10 mg. | | | 5 mg. | | |

could have been given to some of the patients without causing symptoms. This effect of a change in the dose was demonstrated in three patients. Nausea stopped when the dose was cut from 15 mg. to 5 mg. daily. A "driven feeling" reported by a patient taking 10 mg. daily was no longer present when 5 mg. was used. A rash and itching of the skin produced in one patient by 5 mg. daily cleared up on 1 mg. daily. This latter patient, however, had very little relief from her hot flushes on 1 mg. daily although 5 mg. daily gave 50 per cent relief.

Nine patients (6 per cent) had symptoms that were probably not due to the tablets. Three patients were slightly more nervous, but they preferred to continue taking the tablets as they felt better in general. One patient who complained of sleepiness before taking the tablets thought she became a little more sleepy. Three patients complained of gastrointestinal symptoms, but in one case there was gastric ulcer, in another, colitis with similar "attacks" previously, and in the third, "all medicines upset the stomach." It was thought by one patient that the tablets caused hives, but this supposition was probably untrue as urticaria occurred frequently before taking the tablets. One patient complained of a "pressure in the head" which lasted only a short time even though the tablets were continued.

## DISCUSSION

Benzestrol gave most of the patients satisfactory relief of their estrogen deficiency symptoms. This improvement occurred whether the condition was caused by primary or secondary ovarian failure during the menacme, by the natural or artificial menopause or by senility. With this treatment the response was less intense than it was when diethylstilbestrol dipropionate or hexestrol were used. Thus a larger dose was necessary when benzestrol was used instead of the stilbenes, and the amount usually employed ranged from 5 mg. to 15 mg. daily. This dosage gave satisfactory relief to 76 per cent of the patients with the natural menopause and to 87 per cent of those with the artificial menopause. These figures compare favorably with the results previously obtained with other estrogenic substances.[5,6,7,8] While no attempt was made to get 100 per cent improvement in a greater number of the patients by employing larger doses, it was believed possible to do so because some patients responded much better to 15 mg. than to 5 mg. or to 10 mg. However, at times 100 per cent relief was obtained with a 5 mg. dose. If the doses given were not large enough, the treatment was changed to hexestrol or stilbestrol. These drugs were cheaper than benzestrol and their use was practical when a very strong estrogenic effect was required.

Objective proof of the estrogenic potency of benzestrol was demonstrated by vaginal smear tests showing an improvement in cell cornification, by an increase in vaginal moisture, by greater breast fullness and by the production or inhibition of uterine bleeding.

Although not a part of this study, it was found that several patients who were unable to take .5 mg. to 1 mg. of stilbestrol because of severe nausea could take 5 mg. to 15 mg. of benzestrol without nausea. Some patients were nauseated by therapeutic doses of stilbestrol, hexestrol, and benzestrol administered separately, but others were nauseated by only one or two of these substances. Of the three, stilbestrol was the most likely to cause nausea, whereas benzestrol and hexestrol were much less likely to cause it.[5,8]

## SUMMARY

Benzestrol satisfactorily relieved women of the symptoms due to estrogen deficiency. In addition objective proof was obtained of its estrogenic potency. The amount necessary to produce a good therapeutic effect varied from 5 mg. to 15 mg. daily. A few mild toxic reactions occurred with the use of benzestrol, but in this respect it was preferred to diethylstilbestrol dipropionate, which caused a much higher percentage of reactions.

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## REFERENCES

1. Blanchard, E. W., and Stebbins, R. B.: Effects of oral and parenteral administration of new synthetic estrogen, benzestrol, in rat, Endocrinology, 36:297-304 (May), 1945.
2. Blanchard, E. W., Stuart, A. H., and Tallman, R. C.: Studies on a new series of synthetic estrogenic substances, Endocrinology, 32:307 (April), 1943.
3. Freed, S. C., Eisin, W. M., and Greenhill, J. P.: Assay in the human female of synthetic estrogen, 118B, J. Clin. Endocrinology, 2:213 (April), 1942.
4. Greenhill, J. P.: The use and potency of synthetic estrogens, Am. J. Obst. & Gynec., 44:475 (Sept.), 1942.
5. Harding, F. E.: Diethylstilbestrol diproprionate; a clinical comparison with estrone and estradiol benzoate, West. J. Surg., Obst. & Gynec., 50:207 (April), 1942.
6. Harding, F. E.: The oral treatment of ovarian deficiency with conjugated estrogens-equine, West. J. Surg., Obst. & Gynec., 52:31 (Jan.), 1944.
7. Harding, F. E.: Oral substitution therapy with ethinyl estradiol and alpha-estradiol, Am. J. Obst. & Gynec., 48:181 (Aug.), 1944.
8. Harding, F. E.: The oral use of hexestrol for estrogen deficiency, Am. J. Obst. & Gynec., 51:660 (May), 1946.
9. Harding, F. E.: Some allergic reactions to parenteral therapy, Med. Rec., 152:448 (Dec.), 1940.
10. Harding, F. E., and Fraser, A. V.: Use of testosterone pellets in the male hypogonad, Urol. & Cutan. Rev., 46:575 (Sept.), 1942.
11. Hufford, A. R.: The synthetic estrogen octofollin (in oil), J.A.M.A., 123:259 (Oct.), 1943.
12. Jaeger, A. S.: Use of octofollin in conditions of estrogen deficiencies and in gonorrheal vulvovaginitis, J. Indiana M. A., 37:117-119 (Mar.), 1944.
13. Jaeger, A. S., Moenning, W. P., and Bowman, G. W.: Gonorrheal vaginitis, Urol. & Cutan. Rev., 47:81 (Feb.), 1943.
14. Murphy, J. A.: On the employment of octofollin for the relief of menopausal symptoms, for the suppression of lactation, and in gonorrheal vaginitis, Am. J. Obst. & Gynec., 46:146 (July), 1943.
15. Roberts, H. K., Loeffel, E., and MacBryde, C. M.: Octofollin a new synthetic estrogen, J.A.M.A., 123:261 (Oct.), 1943.
16. Stebbins, R. B., and Blanchard, E. W.: Effects of new synthetic estrogen, benzestrol, upon hematopoietic system in rat, Endocinology, 36:305-312 (May), 1945.
17. Talisman, M. R.: A clinical and laboratory study of the synthetic estrogenic substance, octofollin, Am. J. Obst. & Gynec., 46:534 (Oct.), 1943.
18. Taylor, S. G., III, and Thompson, W. O.: Experiences with a new synthetic estrogen for oral administration, Endocrinology, 30:S1042 (June), 1942.