STILBESTROL IN THE TREATMENT OF OVARIAN DEFICIENCY

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A female sex hormone which possesses the properties of the follicular hormone, and which is orally active, highly potent and cheap is of interest to most clinicians. Diethylstilbestrol (stilbestrol) is such a substance. It was first described by Dodds[1,2] and his co-workers. It is one of several related synthetic substances derived from a stilbene nucleus. Its formula is 4:4′-dihydroxy-a: β-diethylstilbene, bearing no relationship to the formula of any known natural estrogen.

Both experimentally and clinically it has been shown to possess many, if not all, of the properties of the natural estrogens. In addition to the form mentioned above, the dipropionate and the acetate have been used.

Stilbestrol in the several forms used clinically has been demonstrated to have the following properties:

1. The production of a follicular type of response in the genital tract of human beings and animals.
2. Inhibition of the excess production of gonadotropic hormone in castrates.[3]
3. Proliferation of the nipples and duct tissue of the breasts.[4]
4. Inhibition of lactation post-partum.[5]
5. Production of secondary sex characteristics in female hypogonadism.[4, 6]
6. Regulation of some cases of menstrual arrhythmias.
7. Relief of various subjective symptoms attributable to ovarian deficiency, such as menopausal symptoms, premenstrual headache and nervous tension, and certain associated states of mental depression and chronic exhaustion.
8. It relieves senile vulvovaginitis and cures gonorrheal vaginitis in children.[7]

Stilbestrol is effective by mouth, by intramuscular injection in oil, in suppositories, and by implantation subcutaneously as pellets.[8] The oral and intramuscular dosage has varied from as little as 0.1 mg. daily to as much as 60 mg. daily. However, doses in excess of 5 mg. daily have not been used often. When given in cases of menstrual arrhythmia, it may be used at times to best advantage in conjunction with progesterone. So-called toxic effects, chiefly nausea, have limited its use in some hands and have discouraged it in others.[3, 9]

METHODS AND MATERIALS

We have administered the drug to over eighty patients. Forty of these whom we have been able to observe carefully have been selected as the

TABLE 1

Case No.	Stilbestrol Daily Dose Mg.		Previous Estrogen Treatment (Estradiol-B given by injection in every case)	Stilbestrol Relieved											Stilbestrol Produced				Remarks
	Initial	Maintenance		Hot Flashes	Headaches	Depression	Irritability	Exhaustion	Psychoneurosis	Breast Pain	Joint Pain	Menorrhagia	Metrorrhagia	Hypomonorrhea	Pruritus	Nausea	Vomiting	Abdominal Distress	Headache	
1	0.25	0.25	Estradiol-B							Yes		Yes								
2	1.0	1.0	Estradiol-B									Yes								
3	0.25	0.25	None				Yes					Yes								Given only with Estradiol
4	0.5	1.00			Yes							Yes				Onset				
5*	0.25	1.00	Estradiol-B		No			Yes												
6	0.5	0.5						Yes												
7	0.5	1.0	Estradiol-B										No			Yes	Yes			Not tolerated
8	0.25	0.5				Yes		Yes												
9	0.5	0.5	Estradiol-B					Par.					No							
10	0.25	1.5																		Hemorrhagic cystitis
11*	1.0	2.0	Estradiol-B	Yes		Yes								Par.				Yes		
12	0.25	2.0			Yes									Yes						
13	0.25		Estradiol-B		Yes											Mild				
14	0.25	0.5			Yes															
15	0.25	0.5	Estrone	Yes																
16	0.75	0.75	Estrone	Yes		Yes			Yes											
17	0.25	1.0	Estradiol-B	Yes		Yes														
18	0.25	0.5	Estradiol-B	Yes		Par.														
19	0.25	0.5	Estrone	Yes		Yes														
20	0.25															Severe				Not tolerated
21	0.1	1.5	Estradiol-B	Yes	Yes			Yes												
22	0.1	0.5	Estradiol-B	Yes							Yes									
23	0.25	0.25		Yes												Onset				
24	0.25	0.75				Yes			Yes											
25	0.25		Estrone	Yes																
26	0.25	0.5		Yes		Yes	Yes	Yes												
27	0.25	0.5		?												Mild				
28	0.5															Severe				Not tolerated
29	0.25	1.0	Estradiol-B		Yes															
30	0.25	1.5	Estradiol-B	Yes	No															
31	0.25	0.5			Yes	Yes	Yes													
32	0.25	0.25					?												Yes	
33	0.25	0.75	Estrone		Par.	Par.														
34	1.0	1.0		Yes					Yes											
35*	0.1	0.5		Yes		Yes														
36	0.5		Estradiol-B											Yes					Yes	Not tolerated
37*	0.5	1.0																		
38	Oint ment														Yes					
39	0.25	0.50	Estradiol-B			Yes	Yes													
40	0.25	0.25				Yes														

Estradiol-Benzoate was in the form of progynon-B, Schering Corp.
Estrone was in the form of Theelin, Parke Davis and Co.
* See text.

basis of this report (Table 1). They have been treated for periods of from one to thirteen months. There were twenty-four menopausal cases, fifteen cases of partial ovarian deficiency of various types, and one case of senile vulvovaginitis. The dosage of stilbestrol given varied from 0.1 mg. to 2 mg. daily. In most cases, the initial daily dose was 0.25 mg., and was increased gradually to 0.25 mg. several times daily, if necessary. Increase in the number rather than in the size of dosages was practiced in most cases. The estrogenic response was studied by means of vaginal smears.

In only two cases was stilbestrol administered intramuscularly; one patient received a single dose of 2 mg. of stilbestrol and was nauseated, weak, and stuporous for thirty-six hours; she subsequently took a therapeutically effective dose by mouth without discomfort (Case 30). The other patient took 0.1 mg. intramuscularly every other day with complete relief of symptoms but she could not maintain this relief constantly on twice that dosage by mouth.

Menopause

These cases include seven of surgical menopause, thirteen with menopausal symptoms and amenorrhea for various periods, and five who had climacteric symptoms but who still were menstruating. The average dose of stilbestrol required for complete symptomatic relief was 0.6 mg. daily. The castrates required only a slightly higher dose than the others.

Seventeen patients complained of hot flashes. Fourteen were relieved completely, and one was not relieved, possibly because of severe hypertension which has been present in others in whom the hot flashes were difficult to ameliorate; two others did not tolerate the drug. Relief of depression and irritability accompanied relief from hot flashes. Headaches were present in four cases; one did not tolerate the drug, one had partial relief, and two had complete relief. Complaints such as exhaustion and irritability, attributable to the menopause, were relieved constantly. Joint pains were relieved by stilbestrol in one case and recurred on its withdrawal. One patient had complete relief of pain of right sciatic distribution both from estrone† and from stilbestrol.

Hypo-Ovarianism

Of fifteen cases of ovarian insufficiency, three were unable to tolerate a therapeutic dose, one had stilbestrol only in conjunction with estradiol benzoate*, seven had marked relief or complete cessation of symptoms, and four showed improvement. Two of the latter probably had insufficient dosages; the other two were cases of anorexia nervosa. In these the

† Theelin, Parke Davis & Co.

* Progynon-B, Schering Corp.

estrogenic response, judged by vaginal smears, was good but the total clinical benefit was slight. The same result had been obtained with large doses of estradiol benzoate.

Symptoms other than disturbances in menstrual flow and rhythm included premenstrual headache and irritability, chronic exhaustion, hot flashes, and decrease in sexual libido. One case had increased libido. Premenstrual headaches were relieved completely in all of four cases, hot flashes were abolished, and other symptoms were affected to a variable extent. Judging by repeated volunteered statements, we have found that stilbestrol produces a feeling of energy and well-being usually equal to that produced by the natural estrogens.

Of the fifteen cases of hypo-ovarianism, seven had menstrual disturbances, not including a case of amenorrhea due to hysterectomy. Four of these exhibited menometrorrhagia, two had irregular scanty periods, and one had regular periods but a scant flow. Of the menometrorrhagias, Case 1 established a regular normal menstrual cycle with the use of 0.25 mg. of stilbestrol daily. Case 2 had a premenstrual endometrium which was of the early regenerative type, the equivalent of a normal endometrium of less than one week's development. Regular menses were established by the cyclic use of stilbestrol-progesterone, simulating the method used by Hamblen[10] and Ryan[11], in the treatment of menometrorrhagia with cyclic estrone-progesterone. The dose of stilbestrol in this case was 1 mg. daily for the first twenty-five days of the cycle, and 2 mg. of progesterone intramuscularly on the twenty-second, twenty-third, twenty-fifth, and twenty-sixth days of the cycle. Case 3 took stilbestrol in conjunction with cyclic estradiol-benzoate-progesterone therapy, and the part of stilbestrol in the successful result cannot be evaluated. Case 4 complained of profuse infrequent periods; following 1 mg. of stilbestrol daily they became more frequent and scant; insufficient dosage was indicated by subnormal vaginal smears and incomplete relief of symptoms. Cases 7 and 11 did not tolerate the drug. Case 12 complained of premenstrual headache and had a regular rhythm; on one occasion during treatment, a period was delayed. Thereafter the drug was regularly withdrawn for one week preceding the menses and the cycle continued regularly.

Discussion

Establishment and duration of effect: The time required for the full therapeutic effect has been variable, due in part to the practice of beginning with small doses and gradually increasing them. Case 35 had marked relief of hot flashes within twenty-four hours after a single intramuscular injection of 0.1 mg. Other cases receiving gradually increasing daily doses have had gradual elimination of symptoms over periods of from one week to two months. Most patients experience sub-

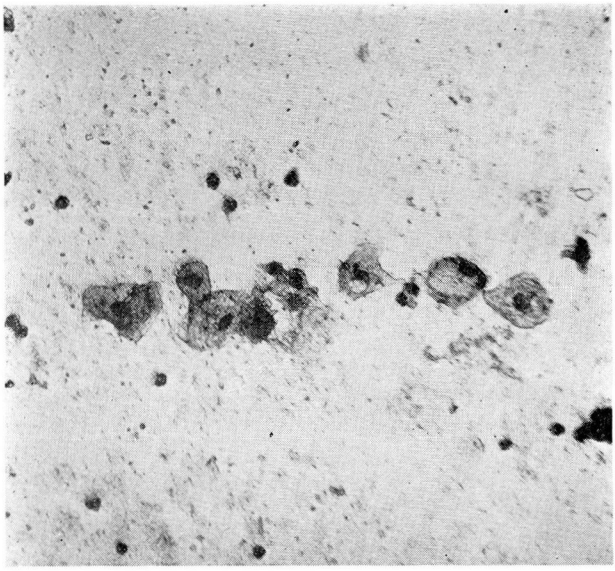

FIGURE 1: Vaginal smear from surgical castrate, untreated. (X225)

jective benefit within three days after beginning stilbestrol therapy and obtain a maximum effect from a given dose within ten to fourteen days.

The time required for a relapse upon withdrawal of the drug has varied in most cases from four days to two weeks. A few have had no recurrence until weeks or months after withdrawal, and some have had

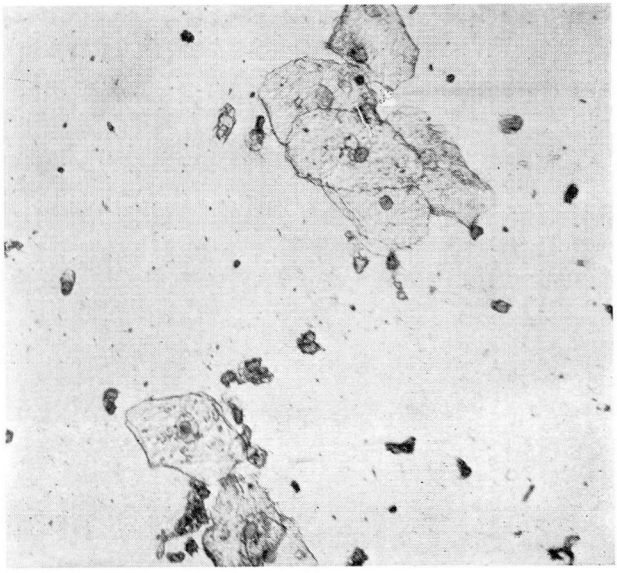

FIGURE 2: Vaginal smear showing partial estrus effect. (X225)

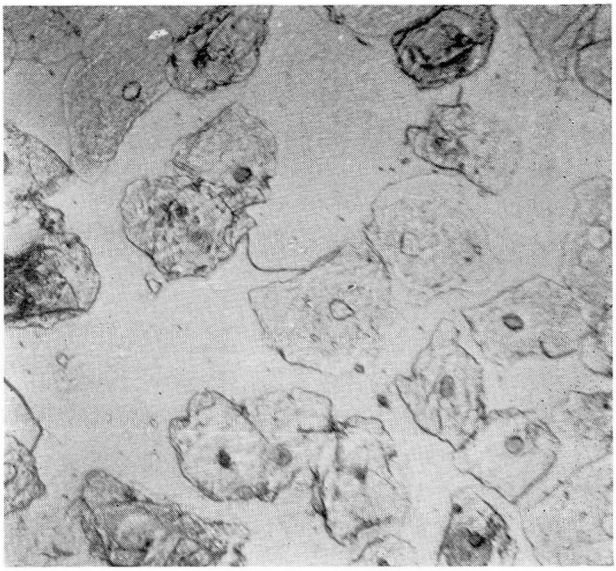

FIGURE 3: Vaginal smear showing full estrus effect. (X225)

no recurrence; obviously, this cannot be due to persistence of stilbestrol activity.

The vaginal smear changes are not so prompt as the symptomatic changes. Relief produced by stilbestrol in one or two days is not reflected in the smear until several days later. Evidence of withdrawal in the smear tends to be slower than the appearance of withdrawal symptoms by one or two weeks. This is similar to the experience of MacBryde et al.[12]

Vaginal bleeding upon withdrawal of the drug occurred in a few cases one to two weeks after stopping the drug. The duration and amount of flow varied; some patients had a heavy flow for as long as two weeks.

Vaginal smear response: Vaginal smears taken after the method described by Papanicolaou[13] have been used as an index of estrogenic effect in nearly all cases. We found it possible to make a rough but satisfactory estimate from immediate examination of the wet smear under a coverslip. A castrate type of smear, consisting of small round epithelial cells with large nuclei and many leukocytes (Fig. 1), is changed readily, by a small dose of stilbestrol, to one showing larger cells with a tendency to polyhedral form and smaller nuclei with a few or even no leukocytes (Fig. 2). A considerably larger dose is required sometimes to bring the smear to an approximately full estrus type, indicated by sharply polyhedral cells with small nuclei having no visible nuclear structure and the absence of leukocytes and debris (Fig. 3). The effective therapeutic dose frequently is less than that required to produce the latter type of

smear. It is probable in some cases, as noted by Shorr[9], that a dose sufficient to produce a full estrus smear cannot be given orally.

We feel that the wet vaginal smear should be regarded only as a rough index of estrogenic effect. If an approximate full estrus type of smear is produced without definite symptomatic relief, the symptoms are regarded as not being due to estrogenic deficiency. When a full estrus type of smear could not be correlated with the symptoms, such symptoms have not been those usually caused by ovarian failure.

Stains of fixed preparations, using the method of Papanicolaou[13] and later that of Shorr[14], have been made routinely in addition to the wet smears. The response as judged by vaginal smears attaining full estrus or slightly less than the full estrus type varies considerably.

The dose of stilbestrol necessary to produce full estrus or slightly less than full estrus response varies considerably in various individuals. It is influenced undoubtedly by the amount of estrogen in the body. In such cases as those illustrated in the following table a nearly complete or complete estrus response was obtained on doses of 2 mg. per day or less and in one on a dose as low as 0.25 mg. per day. The response is graded as 1+ to 4+ on a basis of 4.

TABLE 2

Case	*Age*	*Diagnosis*	*Dose*	*Vaginal Smear Response*
5	31	Hypo-ovarianism	1.0 mg.	3+
12	37	Premenstrual Headache	2.0	3+
13	42	Premenstrual Headache	0.5	4+
16	44	Castrate	0.75	4+
17	35	Castrate	1.0	4+
21	50	Menopause	1.5	4+
26	40	Menopause	0.25	4+
30	57	Menopause	1.5	3+
33	47	Menopause	0.75	3+

Previous therapy with natural estrogens: Twenty-four of our patients received natural estrogens by injection before stilbestrol was given. All cases in which stilbestrol was tolerated obtained the beneficial effects of the natural estrogen. In some of these patients, stilbestrol was gradually substituted for the natural estrogen (usually estradiol benzoate) without symptomatic relapse. No constant dosage was noted in these.

Toxic effects and complications: Early in the study of stilbestrol

severe toxic effects including liver damage were reported to occur in animals.[15] Selye[16] demonstrated the same type of effect following the administration of large doses of natural estrogens. Clinically various unpleasant symptoms and complications have been reported following the use of stilbestrol, usually referred to as toxic effects, although there may be some doubt as to the propriety of the use of the term "toxic." These include nausea, vomiting, abdominal distress or pain, headache, dizziness, cutaneous rashes,[9] paresthesiae, toxic psychosis,[9] hematometra and hematocolpos,[17] and bloody diarrhea.[9] MacBryde,[12] Shorr,[9] and Buxton[18] have performed various laboratory tests including blood counts, urinalyses, blood chemistry and liver function tests following stilbestrol therapy. Aside from the development of albuminuria and casts in one case (Buxton) and some inconclusive changes in liver function (Shorr), all findings were normal.

In our series it was necessary to discontinue the drug because of unpleasant symptoms in five cases (12.5 per cent) and mild untoward symptoms occurred in six others (15 per cent). Three of our patients had severe nausea and two of these had vomiting. In all three, the drug was discontinued after one dose. In four there was mild nausea; one of these had nausea with the use of 0.5 mg. daily but maintained symptomatic relief and avoided nausea by reducing the dose to 0.25 mg. One patient who was taking 0.25 mg. per day had such mild nausea that she did not wish to discontinue the drug. In two patients, mild nausea was reported at the outset only. There may have been more cases in this latter class, for we frequently have refrained from suggesting the possibility of untoward reactions.

Two patients with anorexia nervosa and ovarian deficiency were able to take stilbestrol without any increase in their tendency to nausea. The greatest dose was 0.25 mg. four times daily. One patient had severe arterial hypertension with constant nausea. She took 2 mg. daily without any increase in the nausea.

The other "toxic" manifestations in our cases were headache in two patients, abdominal distress in one, and a hemorrhagic cystitis in one. The latter patient took 0.25 mg. of stilbestrol daily for one week on two occasions, and developed marked frequency and dysuria each time. A hemorrhagic cystitis was found on cystoscopy. Of these four patients, only one was able to continue the drug.

Conflicting reports have been made as to the avoidance of nausea by parenteral injection. That unpleasant symptoms may follow parenteral injection is demonstrated by case 30 cited above. Whether or not the nausea is a toxic reaction, there appears to be no good clinical grounds for considering it an indication of organic injury. Davis[4] gave 10 to 25 mg. of stilbestrol daily to three moribund patients for ten, thirty, and

forty-five days, respectively, and at necropsy could demonstrate no lesions attributable to this therapy. The lethal dose for animals has been found to be many times the effective therapeutic dose[12,16] while the dose required to produce nausea in patients often is near the therapeutically effective one.

While we draw no conclusions from this small series as to the relationship of size of dose to frequency or severity of effects, our impression is that the dose which will produce nausea sometimes is close to the therapeutically effective dose, and that it is wise to begin with small divided doses, and gradually to increase them in order that the therapeutic dose may not be inadvertently exceeded. Injections of natural estrogen may be used for more rapid relief at the beginning of therapy, although this often is not necessary. Since the nature of the so-called toxic effects is not understood, considerable caution in the use of the drug is warranted.

Summary

Forty patients, including twenty-four cases of menopausal syndrome, fifteen of partial ovarian deficiency, and one of senile vulvovaginitis, have been treated with diethylstilbestrol. All of the patients who could tolerate the drug experienced improvement. "Toxic" effects were noted in eleven cases, six of which were able to continue the drug. In twenty-four patients who had previously received estradiol benzoate, stilbestrol reproduced the beneficial effects of the latter in all cases in which it was tolerated.

The use of small doses of stilbestrol at the beginning of treatment is suggested as a possible means of avoiding many untoward reactions.

Illustrative Cases

Case 5: A thirty-one year old patient who had had a hysterectomy developed anorexia nervosa and lost weight to fifty-seven pounds. Estradiol benzoate and forced feeding brought her weight to eighty-eight pounds and strength and energy increased considerably. Vaginal smears changed from a markedly deficient to an approximately normal type. On withdrawal of estradiol benzoate, she experienced weakness, nervousness, and an increased tendency to headache and vomiting. A gradual change from estradiol benzoate to stilbestrol, 0.25 mg. four times daily, was made and symptomatic status and normal vaginal smears were maintained. No increase in the tendency to nausea was produced by stilbestrol.

Case 11: A thirty-five year old patient had a chronic left oophoritis and complained of scanty menstruation, severe mental depression, and hot flashes. Estradiol benzoate, 2000 R. U. (1/3 mg.) three times weekly, caused improvement in symptoms but did not abolish the hot flashes. Stilbestrol, 2 mg. daily, caused symptomatic improvement and relieved hot flashes but caused abdominal distress. A therapeutic oral dose of ethinyl estradiol caused nausea. Improvement was maintained without distress by giving 1 mg. of stilbestrol and 0.15 mg. of ethinyl estradiol daily.

Case 12: A thirty-seven year old patient complained of severe premenstrual headaches and a scanty menstrual flow. The symptoms were partly controlled on 0.25 mg. stilbestrol three times daily, and recurred on withdrawal. By gradually increasing the dose to 0.5 mg. four times daily the symptoms were controlled and the vaginal smears were brought to normal.

Case 30: A fifty-five year old patient with severe arterial hypertension, complaining of many and severe hot flashes for several years, required 50,000 rat units of estradiol benzoate daily together with testosterone propionate* for relief. On one occasion she was given 2 mg. of stilbestrol intramuscularly and exhibited nausea, malaise and stupor for thirty-six hours. At a later date she was given 0.25 mg. of stilbestrol orally daily, gradually increased to 2 mg. daily. This controlled hot flashes and caused no increase in a marked tendency to the nausea which she suffered.

* Oreton, Schering Corp.

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