INHIBITION OF LACTATION BY SYNTHETIC OESTROGENIC SUBSTANCES WITH SPECIAL REFERENCE TO DIENOESTROL*

BY

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The hormone control of lactation was reviewed by Nelson (1936). He concluded that the ovarian hormones, which are present in enormously increased amounts in pregnancy, are necessary for the development of the breasts, but inhibit the secretion of milk. The initiation and maintenance of lactation depend on the anterior lobe of the pituitary. After parturition the oestrogenic hormone ceases to be produced in large amounts, and with this release of control lactation begins. A further factor in the maintenance of lactation is the stimulus of suckling, the mechanism of which is obscure; nor is it known how the oestrogenic hormones inhibit lactation, though it is assumed that they do so by inhibiting the action of the anterior lobe. Folley (1936) showed that when the oestrogenic hormone was administered to the lactating cow, lactation was inhibited and the milk yield was reduced. This effect was temporary and depended on obtaining a high level of oestrogen in the blood. Folley and Kon (1936) studied the effect of sex hormones on lactation in the rat. They found that oestradiol caused a marked inhibition in intact rats, and a definite though less well marked effect in rats ovariectomized on the day after parturition. Testosterone propionate also caused pronounced inhibition, but progesterone and androsterone had no effect.

On the basis of these and similar findings it was suggested that oestrogenic hormones might be used for the inhibition of lactation in puerperal women, and numerous reports of this use of the naturally occurring oestrogens have appeared. Foss and Phillips (1938) obtained satisfactory results in 62 cases with oestradiol (progynon B, Schering), giving a total dose of 10,000 I.U. They found that oestrogenic hormone was also useful for flushed and engorged breasts, relieving the symptoms without interfering with lactation. Lehmann (1938) used progynon B oleosum. He found that 100,000 units given by injection in the first 24 hours post partum inhibited lactation in 91% of cases. Inhibition of established lactation was obtained in 89% of cases with 200,000 units, but in only 50% with 150,000 units. Jeffcoate (1939) gave oestrone by mouth in doses of 2 to 6 mg., gradually decreasing the dose over 3 to 6 days. He found that it was usually necessary to supplement this by 1 to 2 mg. of oestradiol benzoate by injection.

Literature of the Oestrogens

The synthetic oestrogenic substance diethyl-stilboestrol, commonly known as stilboestrol, was first described by Dodds, Golberg, Lawson, and Robinson (1938a). It has since been shown by numerous workers that this substance, and others chemically allied to it, are capable of reproducing the biological and clinical effects of the naturally occurring oestrogens. They can be produced relatively cheaply and are equally as potent when given by mouth as when injected, if not more so. Thus they stand in contrast to the naturally occurring oestrogens, which are generally very much less potent by mouth and are therefore best administered parenterally.

Reports on the use of stilboestrol to inhibit lactation have been published by different workers, including Winterton and MacGregor (1939), Wenner and Joël (1939), Mucklé (1940), Stewart and Pratt (1941), and Mendel, Goldman, and Caire (1941). All claimed satisfactory results in the inhibition of lactation, and some also found stilboestrol useful for engorged breasts. Mucklé stated that although initial success was achieved with 5 mg. 3 times daily for 2 days, the breasts filled up in 40% of his cases in 4 or 5 days and further treatment was necessary. Abarbanel and Goodfriend (1940) discovered, in a study of 315 lactating women, that doses up to 1,000 mg. were well tolerated. They also found that stilboestrol did not inhibit the onset of lactation, and, in doses of 500 mg., did not inhibit established lactation provided the stimulus of suckling was present.

Connally, Dann, Reese, and Douglass (1940) studied the effect of stilboestrol in 200 puerperal women, finding no toxic effect even with large doses. By clinical observation it was shown that the uterus responded to oxytocics more readily and involution was more complete at the 21st day than in a control group. The lochia were not altered. The morbidity rate in the treated cases was 4%, compared with 12.8% in the controls. These workers stated, however, that they were not in a position to recommend the routine administration of stilboestrol for the prevention of puerperal infection. They found that the onset of normal lactation was delayed in the cases receiving stilboestrol, but there were no cases of engorged or painful breasts among their patients.

It has been claimed by some authors that stilboestrol is a highly toxic substance. Mazer, Israel, and Ravetz (1941) reported that 52.4% of their patients vomited while receiving 2 mg. by injection every 4 days; when 2 mg. was given daily by mouth 21.3% vomited. These authors were unable to demonstrate any physical damage to their patients, but in rats and rabbits they found that a dose of 0.5 µg. per gramme of body weight caused necrosis of the liver, kidneys, and adrenals. These toxic effects have not been confirmed in pregnant and puerperal women, either in the present series or by other workers. In the present investigation no toxic effects were found beyond transient nausea in 3 patients. Pregnant and puerperal women, as will be shown, tolerate enormous doses of synthetic oestrogenic compounds—a tolerance which seems to be much greater than that of non-pregnant women.

Testosterone propionate has been used for the inhibition of lactation by Kurzrok and O'Connell (1938), Birnberg, Kurzrok, and Klor (1940), and Siegler and Silverstein (1940). The last-named authors consider that testosterone is better for this purpose than stilboestrol, claiming that stilboestrol causes after-pains and excessive lochia. This does not appear to be the experience of other workers who have used stilboestrol, and the results with testosterone were not, in general, so good as those with stilboestrol.

Triphenylchloroethylene is another synthetic substance that has been found to possess oestrogenic properties. Macpherson and Robertson (1939) demonstrated its oestrogenic properties, and also showed that it could be used for the inhibition of lactation. Of their 12 patients 6 received 4,000 mg. by mouth in 5 to 6 days: complete success was achieved in 4, while 2 had some discomfort in the breasts. The other 6 received 250 to 300 mg. by injection, and complete success was achieved in all of them.

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Present Investigation

This investigation was carried out at the request of the Therapeutic Trials Committee of the Medical Research Council, primarily in order to test the effects of the new synthetic oestrogen γ -di-*p*-hydroxyphenyl- Δ^6 -hexadiene, now known as "dienoestrol." The value of stilboestrol for the inhibition of lactation is now established, and it was therefore decided to compare the effect of stilboestrol and diennoestrol in patients in whom it was necessary to inhibit lactation. Trials were also carried out with the synthetic oestrogenic substance hexoestrol.

Hexoestrol, which is 4:4'-dihydroxy- γ : δ -diphenyl-N-hexane, was first prepared by Campbell, Dodds, and Lawson (1938). The biological effects of this compound were studied by Campbell, Dodds, Lawson, and Noble (1939), and it was considered to have oestrogenic properties similar to those of stilboestrol. The effect of hexoestrol on the uterus of the immature rat was found to equal that of stilboestrol, but in the ovariectomized rat its effect was greater than that of stilboestrol. Clinical trials were carried out with hexoestrol and stilboestrol dipropionate by Bishop *et al.* (1940). They found that these substances were similar in their oestrogenic properties, but the incidence of toxic effects was only 4.5% in patients receiving hexoestrol, while 21.6% of those receiving stilboestrol dipropionate showed symptoms of intolerance.

The chemical and physical properties of diennoestrol have been recorded by Dodds, Golberg, Lawson, and Robinson (1938b, 1939). Campbell, Dodds, Lawson, and Noble (1939), comparing the biological effects of stilboestrol, hexoestrol, and diennoestrol, found that when these substances were given by injection hexoestrol was the most actively oestrogenic and stilboestrol was more active than diennoestrol. Zuckerman (unpublished communication), working on monkeys, found that diennoestrol when given by injection appeared to be less potent than the naturally occurring oestrogens. Diennoestrol is, however, extremely potent when given by mouth. Emmens (1938) found that when this compound was given by mouth to mice it had the greatest activity, relative to subcutaneous dose, of any oestrogen examined up to that time. The present clinical trials have shown that diennoestrol, when given orally, is an extremely potent oestrogenic substance.

Clinical Results

The patients in whom it was necessary to inhibit lactation were mostly those in whom the foetus had been lost because of a stillbirth, abortion, or neonatal death. Lactation was sometimes inhibited for social reasons—e.g., in unmarried mothers who had to "foster" their children. In a few cases very sore breasts and severely cracked nipples made breast-feeding impossible. A case of hydatidiform mole evacuated at the end of the 20th week has been included in the series.

No other treatment was given. The breasts were not bound up, though in a few cases in which the breasts were sore or heavy a supporting brassière was worn. Fluids were given liberally and saline aperients were withheld, the only purgative used being liquid paraffin, supplemented where necessary by cascara.

Ultimate success with regard to lactation was achieved in all cases, though in some it was necessary to repeat the course of treatment. The treatment was not consistent in every instance, as the dose was varied in an attempt to find an optimum. In some cases, also, treatment was not begun until lactation was well established. An attempt to analyse the effect of these variables has been made. The course of treatment usually lasted 5 days, though sometimes it was prolonged for 6 or 7 days. The majority of patients received stilboestrol, and this was generally given in a total dosage of 30 mg., starting with 5 mg. twice daily and diminishing the dose by 1 mg. each day down to 1 mg. twice daily.

Of 134 patients in whom it was necessary to inhibit lactation 81 received stilboestrol, 37 diennoestrol, and 16 hexoestrol. The results with diennoestrol are apparently much less good than those with stilboestrol, but this is partly accounted for by the fact that the new substance was given only in very small doses at first, as its potency was not known.

The clinical results are tabulated below. It must be emphasized that "complete success" is claimed only in those cases

in which there was a total absence of breast symptoms and signs as well as of lactation. Even in the remaining cases there were no severe symptoms, and in some there was only slight fullness of the breasts, lasting a day or two, or slight leakage of milk. The results are shown in Table I.

TABLE I

	No. of Cases	Complete Success	Breast Symptoms or Signs Present	Treatment Repeated
Stilboestrol	81	49	32	20
Dienoestrol	37	15	22	9
Hexoestrol	16	6	10	3

In the case of stilboestrol and diennoestrol the influence of the total dose given is seen in Table II.

TABLE II

Dose in First Course of Treatment	No. of Cases	Complete Success	Breast Symptoms or Signs Present	Treatment Repeated
Stilboestrol : 30 mg. or less	59	35	24	19
More than 30 mg. ..	22	14	8	1
Dienoestrol : 1 mg.	5	1	4	1
2-3 mg.	20	11	9	3
4-5 mg.	12	3	9	5

It was necessary to repeat the course of treatment in about a quarter of the patients, an interval of from 1 to 7 days being allowed between each course. Of the patients receiving diennoestrol and hexoestrol who required more than one course of treatment, all responded satisfactorily to the second course. Of the 20 patients receiving stilboestrol who required repeated treatment, 16 responded to the second course, but in 3 a third course was necessary, while one, who had had a miscarriage at 26 weeks, required a fourth course before lactation was finally inhibited.

So far as can be judged from this short series, there is a suggestion that the optimum total dose of diennoestrol is 2 to 3 mg. in 5 days: better results were obtained with these doses than with larger ones. The small dose tried at first—0.1 mg. twice daily for 5 days—was obviously inadequate. The most satisfactory results were obtained by starting with an initial dose of 0.5 mg. twice daily, and diminishing the dose by 0.1 mg. each day down to 0.1 mg. twice daily.

The influence of parity was also studied, with the results shown in Table III.

TABLE III

	No. of Cases	Complete Success	Breast Symptoms or Signs Present	Treatment Repeated
Stilboestrol : Primigravidae	40	28	12	12
Multigravidae	41	21	20	8
Dienoestrol : Primigravidae	26	6	20	8
Multigravidae	11	9	2	1
Hexoestrol : Primigravidae	11	2	9	2
Multigravidae	5	4	1	1

These results are conflicting, probably because of the comparatively small numbers. In primigravidae, however, it was more often necessary to repeat the treatment.

The effect of the duration of pregnancy is shown in Table IV.

TABLE IV

	No. of Cases	Complete Success	Breast Symptoms or Signs Present	Treatment Repeated
Stilboestrol : 0-20 weeks	4	1	3	0
20-32 "	24	9	15	7
32-40 "	53	39	14	13
Dienoestrol : 20-32 weeks	5	2	3	0
32-40 "	32	13	19	9
Hexoestrol : 20-32 weeks	3	1	2	1
32-40 "	13	5	8	2

It was thus generally found easier to inhibit lactation in the later months of pregnancy.

Table V shows the results analysed according to the time of starting treatment after delivery. Eight cases are omitted from the figures for stilboestrol under this heading. In one of

TABLE V

	No. of Cases	Complete Success	Breast Symptoms or Signs Present	Treatment Repeated
Stilboestrol :				
1st day	53	36	17	16
2nd to 7th day	15	10	5	2
After 7 days	5	2	3	0
Dienoestrol :				
1st day	27	11	16	7
2nd to 7th day	5	0	5	2
After 7 days	5	4	1	0
Hexoestrol :				
1st day	8	5	3	3
2nd to 7th day	6	1	5	0
After 7 days	2	0	2	0

these 120,000 I.U. of benzoestrone had been given to help in the induction of labour after intra-uterine foetal death; a stillborn child was delivered, and a course of 30 mg. of stilboestrol was given with complete success as regards the inhibition of lactation. Two other cases, one of heart disease and pregnancy and the other of pulmonary tuberculosis and pregnancy, received 450 mg. and 390 mg. of stilboestrol, respectively, in an attempt to induce abortion. In the first case this failed, but on the day after abdominal hysterectomy it was necessary to give a further 50 mg. on account of painful breasts. The treatment was successful. The second patient passed the foetus after a bag had been inserted into the uterus. She also had painful breasts on the third day after operative removal of the placenta, but these cleared up in a few days with stilboestrol. The remaining 5 cases were of missed abortion or of intra-uterine foetal death. They received doses of stilboestrol ranging from 10 to 70 mg. before delivery. In one of these lactation was successfully inhibited with 31 mg. of stilboestrol post partum, and there were no breast symptoms. The remaining 4 had painful breasts after delivery, but all responded to further doses of stilboestrol, though in one case it was necessary to give two courses of treatment.

The patient with the hydatidiform mole has been included in this series, as her breasts were very full and painful after evacuation of the mole. There was a good response to 50 mg. of stilboestrol, given over a period of 5 days.

Conclusions

To sum up, it may be stated that, in the respective doses given, stilboestrol was more effective than either hexoestrol or dienioestrol from the point of view of inhibition of lactation and its symptoms, though ultimate success was achieved in every case with all 3 substances. Dienioestrol was at first given in very small doses, in order to test its potency in comparison with that of stilboestrol, which had been in use for some months before treatment with the other substances was started. The optimum dose for treatment with stilboestrol was thus standardized, and so the results with the other substances suffer in comparison. The number of cases treated with hexoestrol was small, and here, too, the doses given at the beginning were experimental, and better results were obtained towards the end of the investigation. This may account to some extent for the disparity in the results given above.

When the influence of the number of pregnancies was studied the results were conflicting. A higher proportion of successes was obtained, especially with stilboestrol and hexoestrol, when treatment was started immediately after delivery, or on the first day of the puerperium, than later on. Symptoms occurred much more often when pregnancy ended before the 32nd week, and the most troublesome cases were those of miscarriage between the 20th and 28th weeks. When stilboestrol was given before delivery it was necessary to continue treatment afterwards, and in 6 out of 7 cases the breasts for a time became full and painful.

In addition to the foregoing investigation 3 patients who desired to continue lactation were treated for engorged breasts. One received 10 mg. of stilboestrol, one 2 mg. of dienioestrol, and one 12 mg. of hexoestrol. No other treatment was given, but suckling was continued. In all the cases the symptoms

subsided within 48 hours and breast-feeding was thereafter normal.

Toxic Symptoms.—It was found that pregnant and puerperal women tolerated the synthetic oestrogenic substances by mouth extremely well. In one case 500 mg. in the aggregate and in another 450 mg. of stilboestrol were given with no toxic effects. Only one patient complained of nausea during treatment with stilboestrol. Two patients had nausea during treatment with dienioestrol. Both were receiving only 0.1 mg. twice daily. One was having sulphanilamide for puerperal pyrexia; the sulphanilamide was discontinued and the symptoms cleared up without interruption of the treatment with dienioestrol. The other patient complained of nausea on one day only, and this disappeared in spite of continuation of the treatment with dienioestrol. In no case was the lochial discharge excessive, so far as could be ascertained. Only 2 patients complained of after-pains. Both were multiparous women who stated that they had had after-pains following previous pregnancies, and they did not consider that their symptoms were any worse during the present confinement. The urine was albumin-free in 34 patients out of 38 in whom the urine was examined before discharge from hospital. The remaining 4 were cases of toxæmia, in which albuminuria persisted; but in no instance could this be attributed to the administration of the oestrogenic substance. Three cases of eclampsia were treated with dienioestrol—2 were free of albumin before discharge from hospital, and in the third there was only a trace of albumin on the tenth day.

Discussion

Before the discovery of these specific substances the standard method for the inhibition of lactation consisted in binding the breasts, restricting the fluid intake, and administering saline aperients. This method has several disadvantages. It is often not successful, and the patient has to endure painful engorged breasts for several days. The symptoms are commonly so severe as to necessitate the administration of analgesic drugs. Restriction of fluids is undesirable in a puerperal woman, and especially so if there is any urinary infection or if sulphonamide derivatives are being given. In the presence of perineal lacerations the administration of strong purgatives is undesirable.

The ideal treatment seems to be the administration of synthetic oestrogenic compounds. The treatment is cheap and is easily given; injections are not necessary and there are no serious toxic effects. The method is uniformly successful, provided an adequate dose is given, although occasionally complete relief is achieved only after repetition of the course of treatment. Success can also be attained with the naturally occurring oestrogens and with testosterone and its derivatives, but these substances have the disadvantages that they are expensive and must be given by injection. There appears to be little to choose between stilboestrol, hexoestrol, and dienioestrol, although in this series fewest breast symptoms occurred in the patients receiving stilboestrol. Hexoestrol has been claimed to be less toxic than stilboestrol, but as puerperal women tolerate stilboestrol so well the advantage of hexoestrol from this point of view is not apparent. In this series hexoestrol seemed to be less potent than stilboestrol when given in similar doses, but the number of patients receiving hexoestrol was small. Bigger doses might give better results. Dienioestrol is a very potent oestrogenic substance when given by mouth, and it is effective in about one-tenth the dosage required for stilboestrol and hexoestrol. This may well be an important factor when questions of expense are considered.

All 3 substances have been successfully used for the treatment of engorged breasts without interfering with lactation. The numbers in this series are small, but are sufficient to suggest that this may be a very valuable extension of the use of the drugs.

As regards dosage, with stilboestrol and hexoestrol the best scheme consists in giving large initial doses—5 mg. twice or thrice daily for 2 days—and then gradually diminishing doses for a further 3 or 4 days. This has a large initial oestrogenic effect, and the drug is gradually withdrawn. With dienioestrol one-tenth of the above dosage is generally sufficient, and, in fact, the best results in this small series were obtained with a total dosage of 3 mg. spread over 5 days.

To complete this investigation it was decided to try the effect of triphenylchlorethylene for the purpose of inhibiting lactation.

These trials are now in progress, and it is proposed to publish the results as a supplement to this paper at a later date.

Summary

The synthetic oestrogenic substances stilboestrol, dienioestrol, and hexoestrol were given orally to 134 patients in whom it was necessary to inhibit lactation: 81 received stilboestrol, 37 dienioestrol, and 16 hexoestrol.

Ultimate success with regard to lactation was obtained in all cases, though in some there were breast symptoms. Forty-nine of the patients receiving stilboestrol, 15 of those receiving dienioestrol, and 6 of those receiving hexoestrol were symptom-free. The symptoms complained of in the remainder amounted to no more than a slight fullness of the breasts or a temporary leakage of milk. These results stand in contrast to the older methods of treatment, with which very hard and painful breasts were often seen.

The results were better when treatment was begun within one day of delivery than when it was started later. They were also better in patients in whom pregnancy had advanced beyond 32 weeks than in those in the earlier months of pregnancy. Cases of pregnancy terminating at between 20 and 28 weeks were especially difficult to treat.

After stopping treatment on the fifth day the breasts filled up in about a quarter of the cases, and further treatment was necessary, but ultimate success was achieved in every case.

Three patients with engorged breasts were successfully treated for this condition while lactation continued normally.

In the dosage tried stilboestrol was more effective than hexoestrol. Dienioestrol is a very potent oestrogenic substance, and success was achieved with one-tenth of the dose required in the case of stilboestrol.

No ill effects from the treatment were noted, apart from complaints of transient nausea in 3 patients.

Synthetic oestrogenic substances are valuable for the inhibition of lactation and for the treatment of engorged breasts. They are cheap and effective, and are easily given by mouth.

The supplies of dienioestrol used in these tests were provided through the Therapeutic Trials Committee of the Medical Research Council by Messrs. Boots Pure Drug Co. Ltd., the British Drug Houses Ltd., and the Glaxo Laboratories Ltd. The British Drug Houses Ltd. also supplied the hexoestrol used.

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In an investigation into the significance of an abnormal electroencephalogram (e.e.g.), Denis Williams (*J. Neurol. Psychiat.*, 1941, **4**, 257) comes to the conclusion that an abnormal e.e.g. in an otherwise normal subject is strong evidence of an inborn constitutional abnormality involving the central nervous system. This abnormality appears to be non-specific, and may show itself in the subject or his offspring as a behaviour disturbance which may be psychoneurotic, psychopathic, psychotic, or epileptic in type. Williams estimates that 40% of epileptics have a normal e.e.g. between fits, but the incidence of the abnormality in epileptics showing more than one type of clinical fit was 90%.

A NEW ASPECT OF DRY PLEURISY

BY

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The class of patients under review is that of young adults who present themselves with a history of pleurisy, usually associated with general malaise, pain on breathing or coughing, often no family history of pulmonary tuberculosis, no sputum, and no abnormal physical signs in the chest except a pleural rub. The radiograph is as a rule within normal limits, and the question arises, What is the cause of the pleurisy and what is the correct treatment of the case?

On the assumption that this pleurisy is tuberculous, it is usual to advise a long convalescence, and then a routine examination of the patient over a period of 6 to 12 months or more, together with sputum examinations and serial radiographs at intervals. In view of our present knowledge this treatment is correct, but economically it is not always possible.

Recently the problem has arisen because the chairmen of the National Medical Service Boards have sent patients with dry pleurisy for an opinion on their chest condition. The question whether they are fit for service has to be considered, and, if they are, in what capacity or group, or whether they should be referred for a further period before a decision is made.

A small series of lipiodol radiographs of patients with pleurisy of uncertain origin has been made, introducing the oil into the affected side; in some cases slight but definite bronchiectasis was shown. It must be pointed out that there was no clinical evidence of bronchiectasis, such as cough, sputum, haemoptysis, or clubbing. Bronchiectasis may give rise to pleurisy, and it is well known that in the dry haemorrhagic type there are often no physical or radiological signs; it was this observation that led to the present investigation.

Bronchiectasis, by definition, means a dilatation of the bronchi. However, the clinical condition of "bronchiectasis" has been expanded to include a variety of allied states, of which the relatively common congenital cystic disease of the lung is a good example. The degree of dilatation does not matter; in the earliest cases the only finding is a demonstration on the bronchogram that the bronchi fail to narrow in their distal parts as they should. It is this minimal type of bronchiectasis that has been found in certain cases.

Lipiodol radiographs were carried out on 24 patients with a history of acute dry pleurisy. In 5 of them bronchiectasis of this slight degree was demonstrated, and in 2 of these the original radiograph suggested an infection of the lung in an area which was later shown to be bronchiectatic.

Case Reports

Case 1.—A man aged 21 presented himself with a history of slight cough and pain in the right side of the chest and right shoulder. The pain was worse on breathing and coughing. There was slight sputum which had no taste or smell, but no haemoptysis. At the onset of his illness he had profuse sweats

FIG. 1A

FIG. 1B

for one or two nights, but there was no record of his temperature. The physical signs in his chest were normal, and a radiograph showed a slight smudge at the right lower zone (Fig. 1A). Three days later he was radiographed again before lipiodol was introduced, and it was found that the opacity had vanished. The bronchogram showed that the bronchus supplying the right