

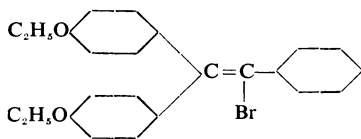
D.B.E.: A NEW SYNTHETIC OESTROGEN

BY

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Robson and Schönberg reported in 1942 the synthesis of the pro-oestrogen *aa*-di-(*p*-ethoxyphenyl)- β -phenyl bromoethylene, the formula of which is



This substance, known as D.B.E., is absorbed from the alimentary tract, but differs from other orally active oestrogens in having a prolonged action whether it is given by mouth or by injection. By experiments with oöphorectomized mice Robson and Schönberg showed that D.B.E. has an oral threshold similar to that of oestradiol and much higher than that of stilboestrol. Its action differs from those of oestradiol and stilboestrol in that a small increase in the dose produces a great prolongation of action. It appears, therefore, that D.B.E. is stored in the body and slowly released. The main site of storage was shown to be the fat (Robson and Ansari, 1943), substantial amounts being present in the body fat of mice a fortnight after administration, by which time it has been eliminated from other tissues.

At first sight it seemed doubtful whether such a substance would be of more than academic interest. Further consideration suggested the possibility that in certain menopausal patients who are liable to hypochondriasis some psychological advantage might be obtained by the administration of a drug at, say, weekly intervals rather than several times a day or even daily. It was therefore decided to investigate the effects in women complaining of severe menopausal symptoms. Such patients are especially suitable for trials of oestrogenic substances, for the effects may be numerically, if roughly, gauged by the number of "flushes" and more exactly by the examination of vaginal smears. During the trial three cases of carcinoma of the prostate became available, and it was hoped that in these the level of serum acid phosphatase might act as a numerical expression of oestrogenic effect. Unfortunately the shortage of staff in pathological laboratories at present made it impossible to carry out this plan completely. The effects were examined also in three cases of uterine atrophy.

Menopausal Patients

Six patients were chosen in whom the only menopausal symptoms were hot flushes. They were all women whose general demeanour and past history suggested that they were mentally stable. It is of interest in this connexion that one patient, not included in the series, was entirely unrelieved by D.B.E. and by stilboestrol, but was completely cured by phenobarbitone.

Each patient was given an inert tablet for a month before the trial and the daily flushes were counted. The daily average was in no case significantly affected by "dummy" treatment.

Case 1.—Average in the control period, 20 flushes a day. Preliminary experiments with doses of from 0.1 g. and upwards showed that clear-cut results were not obtained with a single dose of less than 1 g. A dose of 1 g. was followed four days later by a steady fall in the number of flushes, the improvement reaching a maximum in a fortnight. A maintenance dose of 300 mg. weekly kept the flushes at the intended level of about 4 a day. Of late, on the same dose, they have averaged 2 a day.

Case 2.—Average in the control period, 22 flushes a day. Preliminary experiments with doses of from 0.5 g. and upwards showed that satisfactory results were not obtained with a single dose of less than 1 g. This dose was followed by an immediate fall to an average of 3 flushes a day, which was maintained for 3 weeks. A maintenance dose of 300 mg. weekly maintained the flushes at an average of 5 or 6 a day, though an occasional additional loading dose has been needed.

Case 3.—Average before treatment, 18 flushes a day. The effect of a single dose of 1 g. was studied. The improvement was not

evident until the beginning of the second week, but continued steadily for 6 weeks, when a sudden deterioration occurred. Daily vaginal smears showed an improvement, beginning on the sixth day. They became normal on the eighth day, and despite continued flushes remained substantially normal until the clinical deterioration set in, this deterioration being "mirrored" by the histological appearances. The deterioration was stopped by 500 mg., and a maintenance dose of 300 mg. has been needed.

Case 4.—This patient had originally been treated successfully with another oestrogen and had relapsed after cessation of treatment. She was having about 4 flushes a day. One gramme of D.B.E. was given. An improvement began in a few days, and, with a maintenance dose of 200 mg. weekly, flushes entirely disappeared in 10 days. When the maintenance dose was reduced to 100 mg. the flushes gradually reappeared in the succeeding fortnight.

Case 5.—Before treatment this patient had only 2 or 3 flushes by day but was greatly disturbed at night, when the flushes at the best occurred 4 times and at the worst were almost continuous. She was given 1 g. of D.B.E. with no maintenance dose. Improvement began in 3 days, and in the second week the flushes averaged 2 in the 24 hours. This state was maintained for a further fortnight, when a gradual deterioration set in. The loading dose was repeated, and she has remained well on a maintenance dose of 200 mg. weekly.

Case 6.—Before treatment she had 12 flushes a day. A dose of 1 g. of D.B.E. gradually reduced her flushes. After 3 weeks they averaged 1 or 2 a day. On a maintenance dose of 200 mg. weekly they ceased altogether, but when this was reduced to 100 mg. they reverted in a month to 6 or 7 a day.

Cases of Carcinoma of the Prostate

Case 7.—Aged 76. Admitted to hospital under Mr. R. H. Gardiner complaining of symptoms of prostatic enlargement for only one month. The prostate seemed to be benign. The vasa were tied and a suprapubic cystotomy performed on Oct. 5, 1943. He was discharged and readmitted for the second operation. Cystotomy on Jan. 21, 1944, disclosed that the prostate was malignant and inoperable. He was transferred to a medical ward, where further investigation failed to reveal the presence of metastases. The serum acid phosphatase was 3.0 units per 100 c.cm. He was given 1 g. of D.B.E. The S.A.P. was re-estimated by Dr. Douglas Robertson at frequent intervals until April, 1944, when shortage of staff made a continuation impossible. During this time he received no additional D.B.E., as it was hoped that the biochemical estimations would indicate the necessary frequency of administration. He began to micturate per urethram; the suprapubic opening closed, and he was discharged in good order on March 8, 1944. When it became impossible to continue the frequent S.A.P. estimations he was given 1 g. of D.B.E. and a weekly maintenance dose of 200 mg. He remained well until Jan., 1945, when he began to have dysuria and frequency of micturition with occasional incontinence. These symptoms increased in severity and he was readmitted on Feb. 20. There was no change in his clinical condition, and skiagrams still failed to show any metastases. His S.A.P. had, however, risen to 14.4 units. His urine was grossly infected with *B. coli*. When this had been treated he became symptom-free and insisted on going home. Meanwhile he was given 3 g. of D.B.E. with a maintenance dose of 0.5 g. weekly. The S.A.P. dropped only to 12.0 units and thereafter rose again. The maintenance dose was then increased to 1 g. weekly, but with little effect. On June 8 a change was made to 5 mg. of stilboestrol three times a day. On July 2 the S.A.P. was 4.3 units per 100 c.cm.

Case 8.—Aged 70. This patient was admitted on June 16, 1942, with the symptoms of enlarged prostate. Carcinoma was suspected, for he had severe pain in the lower part of the back and in the thighs. The skiagrams showed osteo-arthritis only, and the S.A.P. was 0.9 unit. The prostate was enucleated by Mr. Gardiner, and was found by Dr. R. W. Scarff to show an area of spheroidal-celled carcinoma. He was given 1 g. of D.B.E. with a maintenance dose of 200 mg. weekly, and has remained free from prostatic symptoms since. Skiagrams show no secondaries, and the S.A.P. has remained normal.

Case 9.—Aged 51. The patient was under treatment for post-operative pneumonia following appendicectomy. There had been no symptoms of prostatic enlargement before his admission, but while in bed in hospital he began to have slight difficulty in beginning micturition and to complain of backache, which rapidly became very severe. The prostate did not seem to be enlarged, but it was hard. Skiagrams showed extensive secondaries in the pelvis, sacrum, lower lumbar vertebrae, and ribs. The S.A.P. was 46.2 units. Treatment was begun with 1 g. of D.B.E. Relief from pain was satisfactory for a day or two after each dose, but gradually increasing doses up to 5 g. weekly failed to prevent a steady rise in the S.A.P. After seven weeks it had risen to 105 units. D.B.E. was stopped and 5 mg. of stilboestrol t.d.s. given instead. The S.A.P. fell to 8.9 units in three weeks.

Patients with Uterine Atrophy

Case 10.—Her periods began at 14 and occurred regularly for 3 days at intervals of 30 days until the birth of a child at the age of 23. After 10 months of lactation, menstruation was again normal for three years. It then ceased, and had not occurred for 17 months before her first attendance. The uterus was found to be very small. Treatment with D.B.E. was begun, but soon afterwards she received serious injuries in an air raid and was lost to view. In Oct., 1944, treatment was begun again with 1 g. of D.B.E. and a weekly maintenance dose of 200 mg. Treatment for 5 months produced neither menstruation nor increase in size of the uterus.

Case 11.—Since the menarche began at 14 the periods had occurred at irregular intervals of 2 to 6 months. The uterus was minute and the physical make-up suggested hypogonadism. A loading dose of 1 g. of D.B.E. with a maintenance dose of 200 mg. weekly produced no change in three months. During the succeeding three months she was given 5 mg. of oestradiol benzoate intramuscularly twice weekly. The uterus increased in size and menstruation occurred more frequently. A change to oestradiol benzoate, 5 mg. twice weekly during the first fortnight only of the intermenstruum, produced regular menstruation, which has been maintained less regularly since cessation of treatment.

Case 12.—This patient complained of dysmenorrhoea. The menarche had begun at 11 and menstruation had occurred for 5 days every 21 to 56 days. It was very scanty. The uterus was minute. During a period of a year a total of 12 g. of D.B.E. was given. Her menstruation became distinctly more regular (3-4/28-33), but the dysmenorrhoea was not relieved and the size of the uterus was only doubtfully increased.

Toxic Effects

D.B.E. is of very low toxicity. Two menopausal patients treated with the substance felt sleepy on the day after each administration. The symptom was not regarded as serious by the patients, and was mentioned only in answer to a leading question. Lassitude occurs occasionally during the administration of other oestrogens. Only one patient complained of nausea. This symptom occurred on the same day as the administration of the loading dose, and was not severe. The patient who received 5 g. a week had no unpleasant symptoms. Uterine bleeding, leucorrhoea, and headache were not reported.

Discussion

It is clear from the results obtained in six patients suffering from the vasomotor symptoms of the climacteric that D.B.E. given orally is an effective oestrogen with a prolonged action. A loading dose of 1 or 2 g. brought relief of symptoms for two or three weeks. The good effects can be maintained by a weekly dose of 100 to 300 mg.

Less satisfactory results were obtained in three cases of uterine atrophy; but little can be learned from this, for the response of this condition to other oestrogens is very uncertain. D.B.E. failed in carcinoma of the prostate. One of the three patients has remained well for three years, but his prostate was removed at so early a stage of the disease that it is possible to ascribe his good health to the operation rather than to the medical treatment. The other two patients showed no significant improvement under treatment with D.B.E., but responded dramatically to stilboestrol.

This failure may be due to insufficient dosage. It is possible to judge this question by two criteria—comparison with stilboestrol or comparison between the two classes of patient. It is difficult to compare the effective dose of two oestrogens which are absorbed and destroyed or excreted at different rates. Judging from mouse experiments (Robson, personal communication) it would seem that from 20 to 50 times as much D.B.E. is required to produce the same effect as stilboestrol, but allowance must be made for species differences. Taking this figure with reservations, it would appear that at the time of maximum dosage one patient with carcinoma of the prostate was having the equivalent of 80 to 200 mg. of stilboestrol a week and the other 200 to 500 mg. Both responded dramatically to about 100 mg. of stilboestrol weekly. Moreover, one was given about four times and one about ten times the amount required to relieve menopausal symptoms and to change the vaginal smear. It must be remembered that some menopausal women are relieved by extremely small doses of oestrogens, but, taking the two criteria together, it seems unlikely that the dose was too low in the carcinoma cases. The possibility should be borne in mind that there may be a sex difference in the rates of absorption of oestrogens, so that a dose sufficient to treat

a woman may be insufficient for a man. No data on this question seem to exist. It should also be remembered that D.B.E. is not strictly an oestrogen but a pro-oestrogen, and that pro-oestrogens may be less effective than oestrogens in the control of carcinoma. The oestrogenic effect of a pro-oestrogen depends not only on the dose but on the rate of its conversion into an oestrogen. An increase in the dose beyond the amount which can be converted by the body would not produce any increase in the oestrogenic effect. It may well be that the body is capable of converting from pro-oestrogen to oestrogen, a sufficient amount to deal with menopausal symptoms, but not enough to control carcinoma of the prostate, which probably demands a higher oestrogenic level. Robson (personal communication) has found that the administration of large doses of D.B.E. to oophorectomized mice does not induce mating, whereas large doses of oestrogens (for example, oestradiol and triphenyl-chloroethylene) do so. Since the oestrogenic level necessary to induce mating is about 200 times that necessary to produce vaginal cornification, it seems probable that in this experiment the D.B.E. was not converted into an oestrogen at a sufficient rate to produce the concentration necessary for mating. A similar failure may be the explanation of the ineffectiveness of D.B.E. in controlling carcinoma of the prostate.

D.B.E. is a substance of great theoretical interest, but in some respects it is inferior to the other synthetic oestrogens, and it is doubtful whether the advantage of weekly over thrice-daily administration is sufficient to warrant the general introduction of yet another.

I would like to express my gratitude to Prof. McIntosh, Dr. Douglas Robertson, Dr. John Murray, and Mr. R. H. Gardiner for their collaboration, and to Dr. A. N. Macbeth, of Organon Laboratories, for supplies of D.B.E.

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D.B.E. IN TREATMENT OF MENOPAUSAL SYMPTOMS

BY

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The chemical and pharmacological properties of this new synthetic oestrogen are summarized in the accompanying paper by Dr. Raymond Greene. The aims of the work described in that paper were: (1) to confirm that the prolonged action of D.B.E. occurs in the human subject; and (2) to establish a dosage suitable for clinical use.

My own aspect of the work has been confined to patients suffering from symptoms due to the premature cessation of ovarian function brought about by surgical and radiological means. Some degree of selection was used in choosing the subjects. This was done as follows. Twenty-five case records were selected at random—7 of these were discarded as they were not experiencing menopausal symptoms at the time; 4 were rejected because they lived more than 20 miles from Newcastle and it was felt that they might not attend regularly on this account.

Fourteen attended, and were offered treatment for their "hot flushes." No previous therapy with oestrogens had been given to any of them. For the first four weeks these patients were treated with inert tablets consisting either of 15 gr. (1 g.) of cane sugar or of 10 gr. (0.65 g.) of household flour coated with chocolate. On a chart provided for the purpose they kept a record of the number of flushes experienced. Three of the patients were relieved by these tablets and were dropped from the series.

The remaining 11 had no relief, and the weekly total of flushes remained constant. 10 patients were given an initial dose of 1 g. D.B.E. and one severe case received an initial dose of 2 g. 8 of the 11 had some reduction in the number of flushes one week after the administration, but only in two mild cases was the response pronounced. One of these, which