ETHINYL OESTRADIOL

BY

T. N. A. JEFFCOATE, M.D., F.R.C.S.Ed., F.R.C.O.G. URSULA M. LISTER, M.D., M.R.C.O.G.
 BETTY HARGREAVES, M.B., Ch.B., M.R.C.O.G. AND H. ROBERTS, M.B., Ch.B., D.Obst.R.C.O.G.

(From the Department of Obstetrics and Gynaecology, University of Liverpool)

Ethinyl oestradiol is an orally active oestrogen first prepared by Inhoffen and Hohlweg (1938). It is a derivative of alpha oestradiol, the chemical structure of the two substances being very similar.

It has already received quite an extensive clinical trial, particularly in the U.S.A., but has not been available in this country until this year. Reports on its biological actions and therapeutic value have been published by Clauberg and Üstün (1938), Salmon and others (1941), Groper and Biskind (1942), Soule (1942, 1943), Watson (1942), Lyon (1944), Allen (1944), Harding (1944), Bickers (1946), Wiesbader and Filler (1946), and Birnberg and others (1947). These deal with its effects in women, and indicate that ethinyl oestradiol behaves like other oestrogens in its effect on the female genital tract and breasts, including relief of climacteric symptoms and suppression of lactation. Other reports, such as those by Lawrence and Werthessen (1942), Kearns (1942), Huggins and McDonald (1945), and McCrea (1946), go to show that ethinyl oestradiol also has the expected effect on conditions in the male such as carcinoma of the prostate and haemospermia.

Ethinyl oestradiol has reached this country with an already established reputation for being an effective oestrogen and, moreover, one which even when administered orally is extremely potent. Estimates of its activity vary considerably, but all observers agree that it is the most potent oestrogen so far discovered. Inhoffen and Hohlweg (1938) reported it to be 15 to 20 times as powerful as alpha oestradiol when both are administered by mouth. Harding (1944) found it at least 15 to 30 times, and Soule (1942) 50 to 70 times, as active as alpha oestradiol. Allen (1944) estimated it to be 26 times as active as stilboestrol. Soule (1943) said it is 5 to 20 times as powerful as stilboestrol, but Harding (1944), like Allen (1944), puts this figure at 5 or 6. Most of these estimates appear to be based on its capacity for relieving menopausal symptoms, but Bickers (1946) concluded that in the treatment of anovular uterine haemorrhage 0.3 mg. of ethinyl oestradiol is equivalent to 5 mg. of stilboestrol.

When advance supplies of ethinyl oestradiol were put at our disposal* it was decided to undertake a clinical trial, partly to confirm its value as an oestrogenic agent but mainly to assess its potency. For this purpose inhibition or suppression of lactation was chosen as the test object as it seemed preferable to the relief of climacteric manifestations, where the interplay of psychogenic factors makes the assessment of results difficult. An attempt was made to compare the potency of ethinyl oestradiol and stilboestrol, both being administered orally, and to determine within practical limits the minimal dose of each which is required to inhibit lactation. This latter is extremely difficult, if not impossible, to do with any degree of accuracy, because it varies with the spacing of doses and the number of days over which it is administered and the susceptibility of individual patients. For the purpose of this investigation the usual procedure consisted in starting treatment within twenty-four hours of delivery and in giving gradually decreasing amounts of oestrogen over the course of seven days. In a few of the later cases the duration of treatment was reduced. With a few exceptions the patients were observed for ten to fourteen days only, so any very late relapse will not have been recorded unless it was specially reported by the patient. No other treatment such as saline aperients and restriction of fluid intake was given. The results are classified into:

- Excellent.—No sign of breast activity at all.
- Good.—Not more than slight secretion or slight fullness of the breasts for one or two days. No discomfort.
- Fair.—Moderate secretion or fullness without gross engorgement and insufficient to cause the patient more than minimal discomfort.
- Poor.—Varying degrees of engorgement or free secretion of milk, sometimes necessitating a further course of oestrogen therapy.

This type of assessment is similar to but not identical with the one used by Birnberg and others (1947).

Trials with Ethinyl Oestradiol

Ethinyl oestradiol is supplied in tablets, each containing 0.05 mg. active substance, for oral administration. The schemes of dosage employed and the results are set out below. Treatment was started within twenty-four hours of delivery, except when otherwise stated.

Scheme 1.—Technique: 5 tablets b.d. first day, 4 b.d. second day, 3 b.d. third day, 2 b.d. fourth day, 1 b.d. on each of the fifth, sixth, and seventh days of treatment; total, 34 tablets

*We are indebted to Dr. W. J. Tindall, of Organon Laboratories, for a liberal supply of ethinyl oestradiol.

(1.7 mg.). *Results* : Eleven patients treated ; ten did not have any sign of breast activity, while the other one noticed slight secretion on the tenth day. (10 excellent, 1 good.)

Scheme II.—Technique : 4 tablets b.d. first day, 3 b.d. second day, 2 b.d. third day, 1 b.d. on the fourth, fifth, sixth, and seventh days of treatment ; total, 26 tablets (1.3 mg.). *Results* : Eleven patients treated, nine with excellent result ; the tenth had a little fullness and minimal discomfort in the breasts on the fifth day, while the remaining one, a girl of 14, had no breast activity whilst in hospital but is reported to have developed severe pain in the breasts on the fourteenth day, the condition developing into a breast abscess which had to be drained. Not having seen the patient at the time, we are unable to say whether she suffered engorgement of the breasts or whether the condition was an acute mastitis from the time of onset of the symptoms. This case is recorded, however, as showing a poor result. (9 excellent, 1 good, 1 poor.)

Scheme III.—Technique : 2 tablets b.d. first and second days, 1 tablet b.d. third and fourth days, 1 tablet daily on the fifth, sixth, and seventh days of treatment ; total, 15 tablets (0.75 mg.). *Results* : (a) Eight cases ; excellent result in all. (b) A second group of seven patients whose babies died after birth were treated by this technique, starting later than the first day after delivery, often when lactation was already established. The results in this series were as follows :

Case	Treatment Started	Result
1	4th day of puerperium	Excellent
2	5th " "	"
3	3rd " "	"
4	2nd " "	"
5	3rd " "	"
6	3rd " "	Poor
7	3rd " "	Excellent

Scheme IV.—Technique : 1 tablet b.d. for first four days, and 1 tablet daily on the fifth, sixth, and seventh days of treatment ; total, 11 tablets (0.55 mg.). *Results* : Nineteen patients treated. Excellent result in 14 cases (4 patients not observed personally after the fourth day) ; good result in 2 cases (1 patient not observed personally after the seventh day) ; fair result in 2 cases ; poor result in 1 case.

Scheme V.—Technique : 1 tablet b.d. for four days ; total, 8 tablets (0.4 mg.). *Results* : Two patients treated, both with excellent result.

Scheme VI.—Technique : 2 tablets b.d. on first and third days only ; total, 8 tablets (0.4 mg.). *Results* : Two patients treated ; one excellent and one fair result.

Scheme VII.—Technique : 1 tablet daily for four days ; total 4 tablets (0.2 mg.). *Results* : Three patients treated ; two good and one fair result.

Scheme VIII.—Technique : 1 tablet daily on first and third days only ; total, 4 tablets (0.2 mg.). *Results* : Three patients treated ; one good and two poor results.

From our observations on the treatment of the whole series of 66 patients it is clear that ethinyl oestradiol, as judged by its ability to inhibit or suppress lactation, is an extremely powerful oestrogen. If it is administered orally in divided doses, in gradually decreasing amounts, over the course of seven days, a total of 0.75 to 1.3 mg. is sufficient to ensure good results in a high proportion of cases, if not all. A total of 1.7 mg. produces consistently good results and is probably an unnecessarily high dose. The response was excellent or good in 29 out of 30 women who received 0.75 mg. or more and when the treatment was begun within twenty-four hours of delivery. Nevertheless, judging by the general experience with other oestrogens, it is almost certain that if the number of patients had been larger there would have been included a few who were less susceptible and an occasional poor result would have been recorded. When the dose is reduced to 0.55 mg. a critical level is reached and the treatment may fail or be only partially successful in preventing breast activity. Even so, in a few patients as little as 0.2 mg. appeared to be effective. So far as we can find, the only other workers who have

published detailed results on the ability of ethinyl oestradiol to suppress lactation are Birnberg and others (1947). They gave 1.5 mg. over the course of nine days and noted 74% excellent or good results, 16% fair results, and 10% failures among 145 cases.

Trials with Stilboestrol

It is probably true to say that during the last ten years, and in this country, stilboestrol has been the oestrogen most widely used for suppression of lactation. Various techniques are said to give good results. There is no need to review the literature in full, for this was done by Barnes (1942) and Prescott and Basden (1944). Some writers (Diddle, 1941 ; Gavioli, 1944) claim good results with a single dose of 5 or 10 mg. on the first day ; others have been disappointed with the results of giving 35 mg. Some give as much as 45 mg. daily. There seems to be a wide variation not only in the response of individual patients but in the interpretation of results by different observers. Barnes (1942) gave a seven-day course of decreasing amounts of stilboestrol to 81 patients, the total dose being 30 mg. in most cases, but more than this (up to 50 mg.) in 22 cases. The treatment was not completely successful in 32, although in several of these cases there were signs of only minor breast activity. A repeat course of treatment was necessary in 20 patients in all, but these included only one of the 22 who received a maximum dose. This rather suggests that 30 mg. is barely sufficient to ensure the optimum results, for which 40 to 50 mg. is necessary. This conclusion is probably in keeping with the general experience ; for most clinicians, despite minor variations in technique, seem to give about this amount over four to ten days and are satisfied with the result. It is also borne out by other writers. Diddle, Nagyfy, and Sells (1942) obtained uniformly satisfactory results using 40 to 50 mg., but noted 4.5% failures when the total dose was between 25 and 35 mg. and 40% failures with 10 to 20 mg. Coulton (1947), while controlling a series of cases treated with "meprane," gave stilboestrol to 73 patients and noted 40% failures when the total dose was between 10 and 20 mg., 4.5% failures when he gave 25 to 35 mg., and no failures with 40 to 50 mg.

For several years now we have as a routine given 41 mg. over the course of eight days, the daily dose being 10, 10, 6, 5, 4, 3, 2, 1 mg., and the results on the whole have been good, although, in common with most observers, we have met occasional failures for which a further course of treatment has been necessary ; and even that has sometimes failed. As part of this inquiry it was decided to determine the effects of stilboestrol given in smaller doses. The clinical work of the department is carried out in two hospitals ; ethinyl oestradiol was used for all patients in whom it was indicated in one hospital, and stilboestrol in the other. Both groups of patients were unselected, but the observers were not always the same: this latter disadvantage was counteracted as much as possible by having the details of all the results analysed by an independent worker. The details for the stilboestrol therapy are set out below, treatment being started within twenty-four hours of delivery in all cases.

Scheme IX.—Technique : Consecutive daily doses of 5, 4, 3, 2, 1, 1 mg. ; total, 17 mg. *Results* : Twenty-two patients treated. Excellent result in 2 cases ; good result in 6 cases ; fair result in 6 cases ; poor result in 8 cases (supplementary course of treatment given in four).

Scheme X.—Technique : Consecutive daily doses of 10, 10, 5, 4, 3, 2, 1 mg. ; total, 35 mg. *Results* : Twelve patients treated. Excellent result in 2 cases ; good result in 6 cases ; fair result in 2 cases (both had a supplementary course of treatment, although it was not strictly necessary) ; poor result in 2 cases (supplementary course of treatment given in both).

The second group is very small and the significance of the results is doubtful. The findings in both groups are, however, in keeping with those of other writers, and go to show that a total of 35 mg. or less of stilboestrol is hardly enough to ensure consistently good results, while considerably smaller doses are quite unreliable in their effects.

Relative Potency of Ethinyl Oestradiol and Stilboestrol

So far as the suppression of lactation is concerned, and when both substances are given orally in divided doses for seven days, our findings in admittedly small groups of patients lead us to conclude that 0.55 mg. of ethinyl oestradiol is rather more effective than 35 mg. of stilboestrol. A total of 0.75 mg. to 1.3 mg. gives as good if not better results than we have obtained using 41 mg. of stilboestrol as a routine during several years. As judged by its ability to suppress breast activity in the puerperium, ethinyl oestradiol, weight for weight, seems to be not less than 50, and it may be 70, times as potent as stilboestrol. This estimate is higher than that of other workers who based their conclusions on the treatment of menopausal symptoms. It is of course impossible to be exact in these matters because so many factors, such as the rate of absorption, inactivation, and excretion, enter the picture and may act to the advantage of one preparation when one condition is under treatment and to its disadvantage when put to another use. Stilboestrol, for instance, is utilized and excreted quite rapidly. Its fleeting action may be a disadvantage in the suppression of lactation and may explain why late relapse (i.e., breasts filling and secreting on the ninth or tenth day) is relatively common. Our impression is that cases treated with ethinyl oestradiol are less likely to suffer these late relapses, although they do occur. In this respect the suggestion quoted by Lyon (1944) that ethinyl oestradiol is absorbed and utilized comparatively slowly may be significant. Nevertheless this idea is not supported in any strong degree by Lyon's observation to the effect that menopausal symptoms recurred within one to twelve days (average 5.5 days) of suspending treatment. It was the possibility of ethinyl oestradiol having a prolonged action which prompted the treatment of a few cases by Schemes V, VI, VII, and VIII. The results, however, are inconclusive, and further tests with a few doses widely spaced are being carried out.

It was pointed out earlier that several workers have compared the potency of ethinyl oestradiol with that of alpha oestradiol and have variously estimated it to be 15 to 70 times greater. We have no experience of alpha oestradiol, but Diddle and others (1942) reported that for the purpose of suppressing lactation stilboestrol by mouth and alpha oestradiol in propylene glycol administered sublingually are about equal in effectiveness provided the latter is given at regular and short intervals. If this is so then the comparisons made between ethinyl oestradiol and alpha oestradiol can perhaps be taken to give an approximate indication of the relative potencies of ethinyl oestradiol and stilboestrol.

Toxic Effects of Ethinyl Oestradiol

All writers note that ethinyl oestradiol, like most oestrogens and particularly the synthetic ones, is apt to produce untoward symptoms in non-pregnant women. These include nausea, vomiting, headache and malaise, dizziness, and urticaria. Such symptoms are common and occur in about 10 to 15% of cases when the daily dose is 0.1 to 0.15 mg., and in 20 to 25% when doses of the order of 0.3 mg. daily are given (Harding, 1944; Lyon, 1944; Birnberg, 1947). Reduction of the dose results in disappearance of the toxic manifestations. It would appear that most non-pregnant women can take 0.05 mg. a day without ill

effect, although even this small dose may cause nausea and vomiting in some (Birnberg, 1947). These observations are of interest because it has often been stated that it is the synthetic oestrogens which produce vomiting and that the natural ones do not: ethinyl oestradiol is a derivative of the naturally occurring oestradiol, and yet is as liable as, if not more liable than, synthetic oestrogens to cause nausea and vomiting. They rather favour the view which has long been taken by some workers, that the toxicity of any preparation, natural or synthetic, is dependent on its oestrogenic activity rather than its chemical structure. In our clinical trial no ill effects of any kind were noted.* This is not surprising, because pregnant or recently pregnant women rarely show toxic reactions even when given massive doses of any form of oestrogen. Thus it is well known that as much as 1,000 to 2,000 mg. of stilboestrol can be given within four to seven days without upsetting a puerperal woman. We have confirmed this to the extent of giving 700 mg. in seven days to three patients.

Now that ethinyl oestradiol is becoming freely available in this country it is perhaps relevant to point out that, like other oestrogens, it may have other undesirable side-effects, and the likelihood of these again reflects its high potency. For instance, even in moderate doses it can cause endometrial proliferation to the state of hyperplasia (Wiesbader and Filler, 1946; Birnberg and others, 1947), with resulting heavy uterine losses and a disturbed menstrual cycle (Harding, 1944). Soule (1943) reported that as little as 0.85 mg. given in divided doses can cause uterine haemorrhage in a post-menopausal woman, and Birnberg and others (1947) noted that 20% of women given 0.05 to 0.15 mg. daily for climacteric symptoms developed post-menopausal haemorrhage. In women who are still menstruating 0.05 mg. daily sometimes delays the onset of menstruation or makes the menstrual flow excessive (Lyon, 1944). Also, like other potent oestrogens, ethinyl oestradiol is liable to cause swollen and painful breasts and to lead to deep pigmentation of the nipple and areola. If, therefore, its use becomes widespread—and it is likely to, for the drug is cheap and efficient and can be given by the oral route—the fact that it is extremely potent should be recognized, otherwise it will almost certainly be the cause of many cases of post-menopausal haemorrhage in older women and menstrual disturbances in younger ones. Since 0.05 mg. is equivalent to not less than 1 mg. of stilboestrol and may well be equal to 2 or 3 mg., it is probably too powerful a preparation to use for the relief of climacteric symptoms. The introduction of tablets of weaker strength might obviate this difficulty.

Summary

An account is given of a clinical trial of ethinyl oestradiol—an oestrogen new to this country.

Its ability to suppress lactation in a series of 66 patients is assessed and compared with that of stilboestrol. The results go to show that ethinyl oestradiol is most efficient in preventing activity of the breasts.

A total dose of 0.75 to 1.3 mg. spread over seven days gave good results in 21 out of 22 cases. When the total dose was reduced to 0.55 mg. the results were less satisfactory but rather better than those obtained with 35 mg. of stilboestrol. Since it takes 40 to 50 mg. of stilboestrol to produce good results in a high proportion of cases it is reckoned that ethinyl oestradiol is at least fifty times more active than stilboestrol for the purpose of suppressing lactation.

There is evidence in the literature that it is equally potent in producing other oestrogenic effects; thus when it comes

*Since completing this series of cases we have seen one puerperal woman develop an urticarial rash twenty-four hours after taking 0.55 mg. of ethinyl oestradiol within the space of twelve hours. The rash may or may not have been caused by the drug.

into general use there will be need for caution over dosage, otherwise ill effects such as menstrual disturbances, endometrial hyperplasia, and post-menopausal bleeding, as well as toxic reactions such as nausea and vomiting, will be commonly seen.

We are grateful to the other members of the medical staff of the Liverpool Maternity Hospital and Mill Road Infirmary for allowing us to carry out this trial on their cases.

REFERENCES

- Allen, W. M. (1944). *Sth. med. J.*, **37**, 270.
 Barnes, Josephine (1942). *British Medical Journal*, **1**, 601.
 Bickers, W. (1946). *Amer. J. Obstet. Gynec.*, **51**, 100.
 Birnberg, C. H., Livingstone, S. H., Kurzrok, L., and Sherber, D. A. (1947). *Ibid.*, **54**, 855.
 Clauberg, C., and Ustün, Z. (1938). *Zbl. Gynäk.*, **62**, 1745.
 Coulton, D. (1947). *Amer. J. Obstet. Gynec.*, **54**, 289.
 Diddle, A. W. (1941). *Ibid.*, **41**, 563.
 ———, Nagyfy, S. F., and Sells, R. L. (1942). *J. clin. Endocrinol.*, **2**, 307.
 Gavioli, R. L. (1944). *Bol. Soc. Obstet. Ginec. Buenos Aires*, **23**, 348.
 Abstract in *Amer. J. Obstet. Gynec.*, 1946, **52**, 526.
 Groper, M. J., and Biskind, G. R. (1942). *J. clin. Endocrinol.*, **2**, 703.
 Harding, F. E. (1944). *Amer. J. Obstet. Gynec.*, **48**, 181.
 Huggins, C., and McDonald, D. F. (1945). *J. clin. Endocrinol.*, **5**, 226.
 Inhoffen, H. H., and Hohlweg, W. (1938). *Naturwissenschaften*, **26**, 96.
 Kearns, W. M. (1942). *Wis. med. J.*, **41**, 575.
 Lawrence, C. H., and Werthessen, N. T. (1942). *J. clin. Endocrinol.*, **2**, 636.
 Lyon, R. A. (1944). *Amer. J. Obstet. Gynec.*, **47**, 532.
 McCrea, L. E. (1946). *J. Urol.*, **56**, 697.
 Prescott, F., and Basden, Margaret (1944). *British Medical Journal*, **2**, 428.
 Salmon, U. J., Geist, S. H., Walter, R., and Mintz, W. (1941). *J. clin. Endocrinol.*, **1**, 556.
 Soule, S. D. (1942). *Amer. J. Obstet. Gynec.*, **44**, 684.
 ——— (1943). *Ibid.*, **45**, 315.
 Watson, B. A. (1942). *J. clin. Endocrinol.*, **2**, 447.
 Wiesbader, H., and Filler, W. (1946). *Amer. J. Obstet. Gynec.*, **51**, 75.

MÉNIÈRE'S SYNDROME

SUCCESSFUL TREATMENT BY SURGERY ON THE SYMPATHETIC

BY

E. R. GARNETT PASSE, F.R.C.S.

Surgeon, Ear, Nose, and Throat Department, King Edward Memorial Hospital, Ealing

AND

J. S. SEYMOUR, M.B., B.S.

Ménière first described his syndrome in 1861, but had inadequate knowledge of the underlying aetiology. He reported a case of a patient who died after an acute illness of five days, and described the necropsy findings; it would seem that acute haemorrhagic labyrinthitis was the cause of the syndrome.

By definition Ménière's syndrome is a malady characterized by attacks of rotational vertigo accompanied by a tendency to fall, occurring at irregular intervals and associated with tinnitus and progressive nerve deafness. The attacks are sudden in onset and may occur without warning, and if severe the patient may fall to the ground with great violence. Commonly there is an associated vomiting, which may be of varying severity, sometimes lasting for hours to the point of exhaustion. Accompanying these vestibular disturbances are degrees of cochlear involvement the symptoms of which are tinnitus and nerve deafness. At first the nerve deafness is mild and occurs only with the attacks, but in the later stages of the syndrome it becomes progressively worse and is manifest permanently between the attacks, until finally it is complete on the side affected.

In the earlier stages the patient is free from giddiness between the attacks, but with progression of the syndrome

there is a constant state of dizziness, which is considerably accentuated by any sudden movement of the head.

The tinnitus is variable in type and severity; it may be a pulsating throbbing variety or a high-pitched constant note either singing or hissing in character. There is no known precipitating factor, and the absence of premonitory signs makes the attacks the more distressing, the patient developing a constant dread of the next occurrence; thus a not inconsiderable functional element quite often exists with the syndrome—a fact recorded by Levy, O'Leary, and Furstenberg—and great care has to be paid to detail in the examination in order to determine the degrees of organic and functional symptoms.

Aetiology

Much confusion exists about the exact aetiology of Ménière's syndrome, as evidenced by the considerable volume of literature on the subject and the extreme diversity of views expressed—some substantiated by necropsy findings and pathological investigations, some based purely on clinical observation and empirical therapy, and others founded very largely on assumption. Attributable factors in the literature cover such a wide field as poisoning from lead, mercury, arsenic in alcohol, drugs such as salicylates, circulatory disturbances of hypertension, arteriosclerosis, anaemia, the exanthemata, the chronic infections, syphilis and tuberculosis, virus infections, chronic diseases such as leukaemia, purpura, and pernicious anaemia, tumours of the cerebello-pontine angle, and trauma.

Causative theories are equally diverse, ranging from disturbance of sodium metabolism in the local tissues (Furstenberg) to vascular disturbances. The latter Miles Atkinson describes as the "mechanics" of Ménière's syndrome, and the patients are divided into two groups determined by an intradermal histamine test—a vasoconstrictor group and a vasodilator group, in the ratio of five to one. He then treats them accordingly with nicotinic acid or histamine.

Hallpike and Cairns noted at necropsy a distension of the endolymphatic system, with degenerative changes in the organ.

Anatomical Consideration

The blood supply of the inner ear is derived from two sources. The first, of major significance, is the internal auditory artery, which, as is common knowledge, is a branch of the anterior inferior cerebellar artery; or, less commonly, it may arise direct from the lower part of the basilar artery. This in turn is formed by the union of the vertebral arteries at the base of the skull.

The subsequent course of the internal auditory artery is through the internal auditory meatus, accompanying the auditory and facial nerves to its distribution near the inner ear. This distribution would seem to take various forms according to Nabeya, ranging from an almost equal dichotomous division into cochlear and vestibular arteries to a predominant cochlear artery with smaller branches to the vestibule and vice versa, or a vestibular artery dividing to send branches to both cochlear and vestibule. Siebenmann describes the blood supply as a more or less equal division of the internal auditory artery to both cochlear and vestibular fields of distribution. It would seem that the variability of the distribution of the arteries indicated by Nabeya might well account for the variable degree of association of cochlear and vestibular signs in Ménière's syndrome-complex. This would reasonably fit in with the view held by us that the predominant aetiological factor is one of vasoconstriction, and that the smaller vascular distribution to a particular portion of the organ will imbue