The Role of Estrogen/Progestogen in the Management of the Menopause

Edited by I.D. Cooke

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Preface

The management of the menopause evokes strong feelings in many quarters and the best way for reason to replace emotion is to present data from well-designed scientific studies. Clinical scientists are now applying their skills to the human, providing information on peri-menopausal problems relevant to clinical practice.

It is important for active workers in this field to have opportunities to present their data to a critical audience and consequently a meeting was held at the University of Sheffield in March 1978. All participants are grateful to Ayerst Laboratories Limited for organizing this meeting, and to MTP Press Limited for expediting the publication of the Proceedings.

Only by dissemination of new work directed to problems bearing on clinical management will the subject be advanced. I am sure that this volume will make a useful contribution to discussion on problems of the menopause and I am grateful to all the participants for reproducing their data and for generating such useful and provocative ideas both within and outside of these Proceedings.

I. D. Cooke

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Introduction

M. GAHWYLER

This volume provides results and details of some important research programmes concerned with the investigation of estrogens and progestogens and their applications to post-menopausal therapy. Let me first present the composition and basic features of conjugated estrogens. (Figures 1.1–1.5).

Table 1.1 Average composition of premarin tablets determined by liquid chromatography

Steroid sulphate	*Percentage*
Estrone	48
Equilin	26
17α-Dihydroequilin	17
17α-Estradiol	3
Equilenin, 17α-Dihydroequilenin	6
17β-Dihydroequilin, 17β-Dihydroequilenin, 17β-Estradiol	<1

Developments in the field have come from the use of radioimmunoassays, receptor site studies, ambulatory endometrial biopsies, and investigation of estrogen precursors, such as androstenedione and its extra-gonadal conversion to estrone – a subject of distinct relevance to menopausal problems, including osteoporosis. Similarly, improved techniques of bone mass assessment are currently providing faster and more accurate data on skeletal changes.

Since the early 70s we had felt that these methods should be used in order to progress from the rather pragmatic approach of the 50s and 60s to a broader understanding and a more rational medical management of the post-menopausal woman. While there has been tremendous progress in the field of estrogen research in the past 20 years, we realize that, to this day, large gaps persist in our knowledge. For instance, we still do not know, and cannot predict, why some women go through the menopause without any symptoms at all, some are severely incapacitated and still others develop osteoporosis or endometrial or breast cancer.

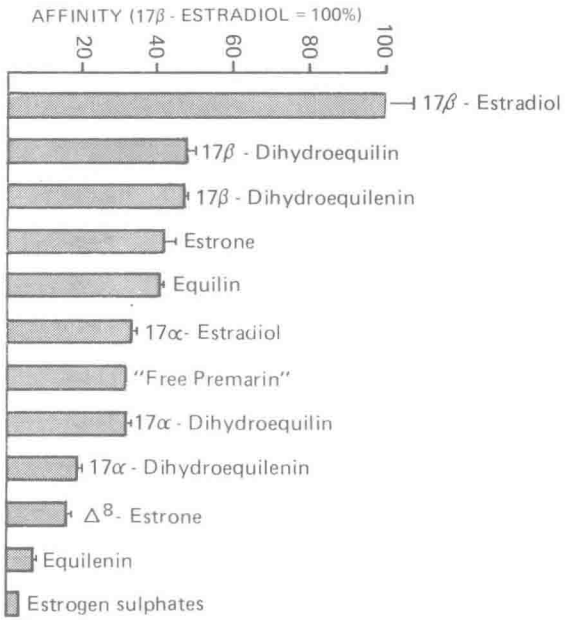

Figure 1.1 Relative binding affinities of Premarin components

The questions of genetic predisposition, endogenous verus exogenous estrogen, receptor sensitivity, androstenedione conversion, hypothalamic imbalance, growth hormone activity, progesterone or rather the lack of it, etc., arise in this context and have been the subject of much recent debate. As with almost everything else in the field, as in cancer research, these matters are not yet clear at all. As Kistner[1] has stated recently, 'The relation of estrogenic substances to

the development of endometrial hyperplasia of all degrees is clear; the relation of these substances to invasive endometrial carcinoma is clouded by assumptions based on individual case reports, retrospective reasoning and uncontrolled experimentation.' In this context, remember that it has not been possible to create in primates – for study purposes – a transformation of endometrial tissue from hyperplasia to malignancy by the administration of exogenous estrogens.

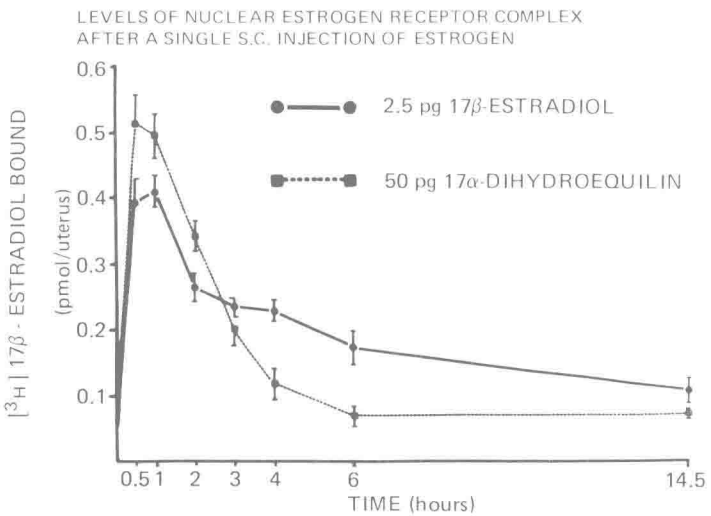

Figure 1.2 *In vivo* uptake of 17β-estradiol and 17α-dihydroequilin in immature rat uterus

The medical problem therefore is much broader than was initially believed and is not limited to the therapy of symptomatic menopausal women. For example, hospital records for Roswell Park Memorial Hospital in Buffalo show that of the total of 450 endometrial carcinoma patients admitted since 1970, only 10 per cent had previously received exogenous estrogens leaving 90 per cent in the untreated group. In the control group the percentage of women treated with hormone replacement therapy[2] was also 10 per cent.

At the Mayo clinic in 10 years, 523 cases of endometrial carcinoma were treated. Only 4.3 per cent 'had used exogenous estrogens of any type, dose or regimen for more than 3 years'[3]. Thus

the main medical and public health concern should not be confined to the relatively small group of women on hormone replacement therapy, but must endeavour also to solve the problems of the remaining 90 per cent.

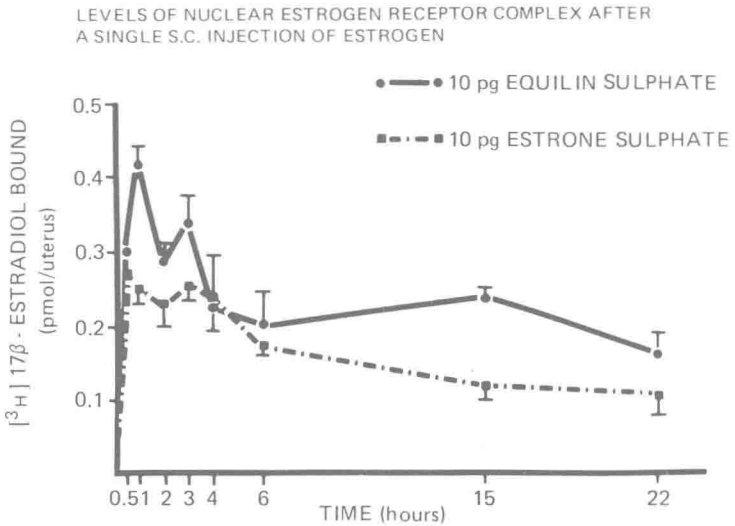

Figure 1.3 *In vivo* uptake of estrone sulphate and equilin sulphate

One other major but salient problem is osteoporosis. According to the recent publication of Heany[4] 25 per cent of all women over 60 years of age have vertebral compression fractures, 80 per cent of all hip fractures occur in patients with osteoporosis, and one-sixth of those cases die within 3 months, whereas the remaining five-sixths constitute an enormous psychological, economic and medical management problem, for the individual, the family and the community at large.

This is a real medical calamity, but one, I believe, that will become avoidable.

To come to grips with these problems: retrospective statistical and epidemiological attempts seem to contain their own built-in contradictions, predicated on study design, selection of controls, etc. Completely opposite conclusions have been advanced by practitioners of these methods, and as such the results seem to be of limited value. On the other hand prospective trials carry their own

inherent difficulties because of the extreme time taken for complications to develop. The only solution is therefore logical clinical research. The fact that these problems affect the total postmenopausal population and not only those on hormone replacement therapy is obviously not new to anyone who has worked in the field. However, I am stating them again, because they have been deliberately and consistently obscured by the media and tendentious medical reporting.

Our primary research aim has attempted to clarify the general metabolic changes and pathology of the menopausal woman, including problems of the menopause not directly associated with estrogen administration. The work presented at this symposium will, it is hoped, lead to the eventual development of a *prospective mode of diagnosis* for all women. By this I mean not only the identification of those patients who qualify for estrogen therapy because of their symptomatology, but also – if not more – for those who have no symptoms whatsoever, but who may – for one reason or another – fall into an 'at risk' category for gynaecological malignancy or osteoporosis. This 'silent' group is composed of at least 80 per cent of the menopausal population.

When we started out with our research programme in 1971 and 1972, I did not envisage that some 6 years later the possibility of a

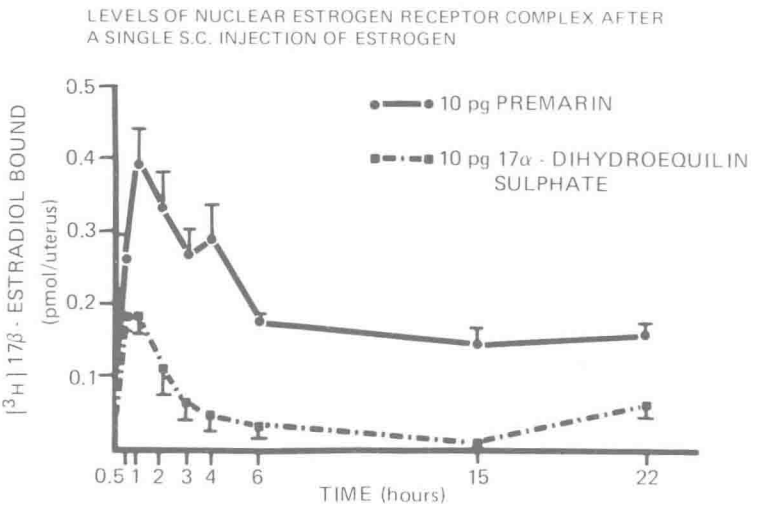

Figure 1.4 *In vivo* uptake of 17α-dihydroequilin and Premarin

prospective diagnosis could advance to within reach in such a short time. Lewis Thomas, President of the Memorial Sloan Kettering Cancer Center in New York[5], put the problem very simply when he stated that we can handle fairly cheaply, from both the individual patient's and the public health point of view, those medical and health delivery problems which are fully understood, whereas the highest costs, to the patient, to the local community and society at large, are occasioned by those disease entities which are still poorly understood. What Thomas makes very clear is that those services

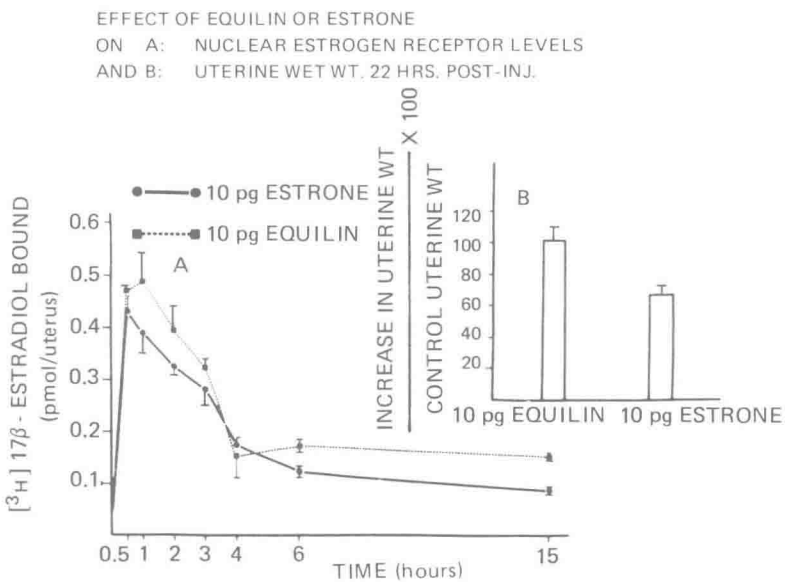

Figure 1.5 Uptake and uterotrophic effects of unconjugated estrone and equilin

which are economically easy to deliver come as a result of what he calls 'the real high-technology of medicine', in other words: medical research.

To conclude, just a few words about another area of research that we are now exploring – I refer to the pursuit of measurable and verifiable effects of the interaction of estrogens and the central nervous system, such as the effects on free tryptophan levels and mental depression, studies on effects of estrogens on sleep, mood and anxiety, and more recently the work on catechol estrogens which are relative newcomers to the list of identified metabolites of 17β-

estradiol[6]. Their role in neuroendocrine mechanisms has begun to emerge only very recently, but the early results have generated much interest. These catechol estrogens occur as a result of an alternative metabolic pathway of estradiol, and exist in a certain balance with estriol via hydroxylation at C-2. It has been shown that this metabolic transformation can occur in the liver as well as in the central nervous system and raises the question of the function of catechol estrogens in neuroendocrine systems. Interestingly enough these catechol estrogens retain only 0.1 per cent or less of the uterotrophic activity of their parent compound, namely 17β-estradiol, but their binding to uterine estradiol receptors is very substantial and long-lasting. Therefore they are particularly real anti-estrogens, and possibly a part of a natural balance and counterbalance system. Some of the properties originally attributed to estriol may be due to these catechol estrogens, a question that certainly will be solved in the future.

References

1. Kistner, R. N. (1978). Estrogens and endometrial carcinoma. Letter to Ed. *Obstet. Gynecol.*, **51**, 2, 255
2. Ambrus, J. Roswell Park Memorial Institute, State University of New York at Buffalo, New York. Personal communication
3. Malkasian, G. *et al.* (1977). Carcinoma of the endometrium, Mayo Clinic experience. *Mayo Clin. Proc.*, **52**, 175
4. Heaney, R. P. (1976). Estrogens and postmenopausal osteoporosis. *Clin. Obstet. Gynecol.*, **19**, 4, 791
5. Thomas, L. (1975). *The Lives of a Cell*, p. 35. (New York: Bantam Books)
6. Fishman, J. (1977). The catechol estrogens. *Neuroendocrinology*, **22**, 4, 363

Discussion

Professor Cooke: Dr Gahwyler showed relative binding affinities. What species did this involve?

Dr Gahwyler: Figure 1.1 was an illustration of an *in vitro* test using rabbit uterine cytosol as the source of the receptors. The next illustrations (Figures 1.2, 1.3 and 1.4) show various binding characteristics based on Anderson's procedures in immature rats. This material was presented at the Second International Meeting on Endometrial Cancer and Related Subjects, held at St Thomas' Hospital in London last March 1977.

Professor Cooke: Could there be different relative affinities in different species?

Dr Gahwyler: It is quite possible. I should be very interested to see the same data repeated in human cultures. In general, animal experiments are fine, but our concern should be with what happens in the human female, not in rabbits.