# CLINICAL RESEARCH

# Dose dependent effects of oral progesterone on the oestrogenised postmenopausal endometrium

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## Abstract

**Oral progesterone 100, 200, or 300 mg daily was given for the first 10 days of each calendar month to postmenopausal women also receiving conjugated oestrogens 1·25 mg daily continuously. Endometrial biopsy specimens were taken on the sixth day of the third or subsequent cycle of combined treatment for histological, ultrastructural, and biochemical evaluation.**

**Secretory histological changes were induced within the endometrium in a dose dependent manner, as were progesterone sensitive ultrastructural features such as nucleolar channel systems, giant mitochondria, and subnuclear accumulations of glycogen. Dose response relations were also observed for suppression of DNA synthesis and nuclear oestrogen receptor, and for induction of the activities of oestradiol and isocitric dehydrogenases.**

**Progesterone administered by mouth clearly provokes an end organ response within the endometrium. Suboptimal effects were observed with the lower doses but progesterone 300 mg daily achieved responses approaching and within the physiological range. This dose may therefore be effective as an alternative to synthetic progestogens for therapeutic purposes.**

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## Introduction

Within the endometrium endogenous or exogenous oestrogens stimulate cell mitosis and proliferation and increase DNA synthesis and the concentration of nuclear oestradiol receptor. Endogenous progesterone in the secretory phase of the ovulatory cycle causes morphological changes within the endometrium. Secretory and ultrastructural features develop and the latter include nucleolar channel systems, giant mitochondria, and subnuclear accumulations of glycogen.[1,2] Biochemically, progesterone exposure exerts an antimitotic or antioestrogenic effect in reducing DNA synthesis and nuclear oestradiol receptor[3] and exerts a secretory effect by increasing the activities of certain enzymes such as oestradiol-17β and isocitric dehydrogenases.[4]

Endogenous progesterone production in normal postmenopausal women is invariably insufficient to produce an endometrial response. But when used in combination with exogenous oestrogens, synthetic progestogens reproduce the characteristic morphological and biochemical changes of the secretory phase of the ovulatory cycle.[5,6] These changes have important clinical implications because they are currently believed to be part of the mechanism whereby the addition of a progestogen to postmenopausal oestrogen treatment reduces the incidence of endometrial hyperplasia and possibly carcinoma, as compared with the incidence with oestrogen treatment alone.[7-9] Unfortunately, the administration of certain progestogens may not be without risk. The increased incidence of hypertension and arterial thromboembolic disease in women taking oral contraceptives has been linked to the progestogen component in a dose dependent manner.[10-12] In the United States the National Institutes of Health appear to have extrapolated these data to the postmenopausal situation and have cautioned against the widespread addition of progestogens to exogenous oestrogen treatment.[13]

Two progestogens widely used with postmenopausal oestrogen treatment, norethisterone and DL-norgestrel, are both derivatives of 19-nortestosterone and as such possess androgenic activity. They increase plasma insulin concentrations,[14,15] which reflects decreased insulin sensitivity and therefore impaired glucose tolerance, and they both lower the concentration of cholesterol in the high density lipoprotein fraction of plasma.[16,17] This is a potentially serious side effect because the incidence of cardio-

vascular disease in both men and women is inversely related to the high density lipoprotein cholesterol concentration.[18 19] Hence the beneficial effects of long term postmenopausal oestrogen treatment in possibly reducing mortality from ischaemic heart disease[20] may be negated by their addition. A progestogen without these metabolic effects is therefore desirable.

Progesterone does not adversely affect plasma high density lipoprotein cholesterol concentrations[21] and causes only minimal changes in carbohydrate metabolism.[22] Although we have reported that 25% of an oral dose of progesterone appears in the peripheral circulation and that plasma concentrations within the luteal phase range are maintained for up to seven hours after ingestion,[23] the belief that oral progesterone is inactive and without end organ effect has recently been restated.[24] We have determined the morphological and biochemical changes within the oestrogen primed postmenopausal endometrium after varying doses of micronised progesterone taken by mouth. For comparative purposes endometrial biopsy specimens were obtained from postmenopausal women during the oestrogen only phase of treatment, and from premenopausal women with the assumption that proliferative phase samples would give an index of physiological oestrogen activity and that secretory phase samples during days 17 to 21 would provide the range of normal progesterone function.

## Patients and methods

Every volunteer was postmenopausal as determined by either a serum follicle stimulating hormone concentration within the postmenopausal range or the presence of typical symptoms of oestrogen deficiency. All patients received conjugated equine oestrogens (Premarin, Ayerst International) 1·25 mg daily continuously (for 365 days a year), with the addition of micronised progesterone (Utrogestan, Laboratoires Besins Iscovesco, Paris, France) for the first 10 days of each calendar month. Three doses of progesterone were used: 17 patients took 300 mg daily (100 mg in the morning, 200 mg at night), 18 used 200 mg at night, and 15 patients took 100 mg at night. These doses were chosen on the basis of the plasma concentrations of progesterone achieved after oral administration.[23]

Curettage was performed on every patient using either outpatient Vabra suction curettage or formal dilatation and curettage under general anaesthesia in the third or subsequent treatment month on the sixth day of combined treatment. Progestational features are maximal at that time.[5 25] The samples were divided according to the following list of priorities: (*a*) tissue for light microscopy was placed into 10% formol saline and (*b*) into 3% glutaraldehyde in 0·1M cacodylate buffer for transmission electron microscopy; (*c*) specimens sufficient for DNA synthesis were placed in Dulbecco's modified Eagle's medium and processed within four hours of collection, while (*d*) samples adequate for determination of enzymatic activities and nuclear oestradiol receptor were immediately frozen on solid carbon dioxide and then stored in liquid nitrogen until analysed.

The endometrial specimens were assessed histologically after staining with haematoxylin and eosin. Fragmented detached epithelium and glands were considered unreliable for assessment and special care was taken to exclude basal layer, isthmic, and endocervical tissue. Features assessed were those of the normal menstrual cycle. In the absence of any secretory features, small glands with some nuclear stratification were classified as proliferative when mitotic figures were seen or as non-secretory when mitoses were absent. In very small sections it was sometimes difficult to distinguish non-secretory glands from a poorly developed late secretory pattern: doubtful cases were classified as non-secretory.

Endometrial hyperplasia and atypia were assessed by the presence of (*a*) abnormalities of tissue architecture including an increased ratio of glands to stroma and cystic or adenomatous features and (*b*) cell hyperplasia including increased stratification, tufting, and nuclear atypia. Assessments were sometimes difficult in small specimens, however, and minimal changes confined to one small area of the specimen were not diagnosed as hyperplasia.

The morphological changes within the endometrium were assessed using a simple scoring system. Subnuclear glycogen is deposited just before and giant mitochondria develop immediately after ovulation in the normal ovulatory cycle. Nucleolar channel systems become visible three days after ovulation and remain for three or four days.[1 2] The presence of each of these features in the postmenopausal endometrial samples was accorded a score of one point, and no score was given when they were absent. Early secretory changes observed by light microscopy also scored one point if present.

DNA synthesis was measured as described[3 26] and is expressed for epithelium as the number of cells labelled per 100—that is, the labelling index; stromal DNA synthesis is expressed as the number of labelled cells per high power field (magnification × 100). Nuclear oestradiol receptor and the activities of oestradiol-17β and isocitric dehydrogenases were also measured as described.[26 28]

The lower limits of sensitivities of the biochemical assays were as follows: epithelial labelling index 0·2%; stromal DNA synthesis 0·2 labelled cells; nuclear oestradiol receptor 0·2 pmol (54·5 pg)/mg DNA; oestradiol-17β dehydrogenase 9 nmol (2·4 μg) of oestrone formed per mg DNA an hour; and isocitric dehydrogenase 100 nmol (74·5 μg) of reduced nicotinamide adenine dinucleotide phosphate formed per mg DNA a minute. Statistical analyses of the biochemical data were by Student's *t* test.

The morphological and biochemical investigations were performed without knowledge of the treatment regimen.

## Results

The comparative premenopausal and postmenopausal oestrogen only data referred to above are included where appropriate.

### LIGHT MICROSCOPY

Eleven of the 15 patients taking 100 mg progesterone provided endometrium sufficient for accurate assessment. Three samples (27%) showed mild to moderate atypical hyperplasia, and one of these also contained secretory changes. One patient had proliferative endometrium, while a non-secretory pattern was diagnosed in three samples (27%). In four patients (36%) varying degrees of secretory change were seen, ranging from early to late patterns.

Adequate amounts of endometrium were obtained from 13 of the 18 patients taking 200 mg. Three samples (23%) showed a non-secretory pattern, while 9 (69%) of the remaining 10 patients had some early secretory changes mixed with proliferative or non-secretory type glands. The tenth sample showed late secretory features. Endometrium sufficient for analysis was obtained from 12 of the 17 patients taking 300 mg progesterone. Two patients (17%) had a non-secretory pattern, while the remaining 10 samples (83%) showed varying degrees of secretory change, including three with late features. No hyperplasia was diagnosed with the 200 and 300 mg progesterone dosages nor in any of the eight samples obtained between days 17 and 21 in the secretory phase.

### TRANSMISSION ELECTRON MICROSCOPY

Endometrium sufficient for assessment by transmission electron microscopy was obtained from seven patients taking 100 mg progesterone, from 11 receiving 200 mg, and from 12 subjects using 300 mg. The table gives the numbers of samples showing subnuclear accumulations of glycogen, giant mitochondria, and nucleolar channel systems. For example, with 100 mg progesterone three samples contained subnuclear glycogen but giant mitochondria and nucleolar channel systems were absent.

The table also shows the combined scores for these three ultrastructural features plus the presence of secretory changes observed by light microscopy. The score (number of samples showing feature/number of samples examined) for progesterone 100 mg was 8/32 (25%), for 200 mg 27/46 (59%), and for 300 mg 35/48 (73%). Comparative data for samples obtained between days 17 and 21 of the secretory phase were 32/32 (100%). None of these features was present in the proliferative phase in premenopausal samples and during the oestrogen only phase of postmenopausal oestrogen treatment.

### BIOCHEMISTRY

As compared with conjugated oestrogen treatment alone, highly significant reductions in the labelling index were observed with all progesterone doses ($p < 0·001$) (fig 1). With progesterone 200 mg and

*Ultrastructural and secretory features in endometrium of postmenopausal women treated with conjugated equine oestrogens 1·25 mg continuously either alone or with progesterone 100 mg, 200 mg, or 300 mg daily added for 10 days each month. Proliferative and secretory phase data for days 17-21 included for comparison*

| Morphological feature | Proliferative | Secretory (days 17-21) | Conjugated equine oestrogens alone | Conjugated equine oestrogens 1·25 mg daily plus progesterone: 300 mg daily | 200 mg daily | 100 mg daily |
|---|---|---|---|---|---|---|
| Subnuclear accumulations of glycogen | 0/11 | 8/8 | 0/14 | 11/12 | 9/11 | 3/7 |
| Giant mitochondria | 0/11 | 8/8 | 0/14 | 8/12 | 6/11 | 0/7 |
| Nucleolar channel systems | 0/11 | 8/8 | 0/14 | 6/12 | 2/11 | 0/7 |
| Secretory histology | 0/11 | 8/8 | 0/14 | 10/12 | 10/13 | 5*/11 |
| Total score (%) | 0/44 (0) | 32/32 (100) | 0/56 (0) | 35/48 (73) | 27/46 (59) | 8/32 (25) |

*Includes one sample showing secretory histology and mild atypical hyperplasia.

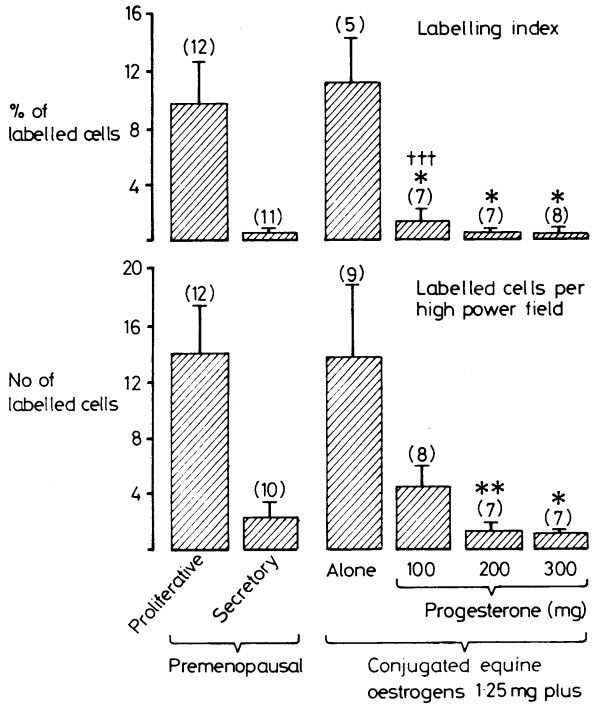


FIG 1—Epithelial (labelling index) and stromal (labelled cells per high power field) DNA synthesis in endometrium of postmenopausal women treated with conjugated equine oestrogens 1·25 mg daily continuously either alone or with progesterone 100 mg, 200 mg, or 300 mg daily added for 10 days each month. Proliferative and secretory phase ranges included for comparison. Results expressed as means and SEM. Figures in parentheses are numbers of observations.

P values (Student's *t* test) represent following significant differences: conjugated oestrogens alone *v* conjugated oestrogens plus progesterone—*p < 0·001, **p < 0·01, ***p < 0·05; conjugated oestrogens plus progesterone *v* premenopausal secretory phase—†p < 0·001, ††p < 0·01, †††p < 0·05.

300 mg the values were not significantly different from the secretory phase range but they were significantly higher with 100 mg ($p < 0·05$). Stromal DNA synthesis was not significantly reduced by the 100 mg dose but was lowered by 200 mg ($p < 0·01$) and 300 mg ($p < 0·001$). With no dose of progesterone was there a significant difference from the values observed in the secretory phase samples. Significant differences in suppression of both epithelial and stromal DNA synthesis were observed between the 300 mg and 100 mg progesterone doses ($p < 0·05$ for both).

Nuclear oestradiol receptor concentrations seen in conjugated oestrogen treated endometria were reduced by all progesterone doses (fig 2), and with the two higher doses this was highly significant ($p < 0·001$). With progesterone 300 mg this reduction was to below the secretory phase range ($p < 0·05$), while with 100 mg the values were significantly higher than those of the secretory phase ($p < 0·05$). The 300 mg dose achieved significantly greater depression of nuclear oestradiol receptor value than did the 100 mg dose ($p < 0·02$).

As compared with oestrogen only treatment, the activity of oestradiol-17β dehydrogenase was significantly increased during treatment with all three progesterone doses ($p < 0·001$) (fig 3). With progesterone 100 mg, however, the values were significantly lower than the secretory phase range ($p < 0·001$). Induction of oestradiol-17β dehydrogenase activity was significantly greater with 300 mg as compared with 200 mg ($p < 0·01$), and with 200 mg as compared with 100 mg ($p < 0·02$).

Isocitric dehydrogenase activity was not increased by the 100 mg dose and was significantly lower than the secretory phase range ($p < 0·001$). Progesterone 200 mg and 300 mg significantly increased isocitric dehydrogenase activity as compared with conjugated oestrogen treatment ($p < 0·01$ and $p < 0·001$, respectively) and also as compared with the 100 mg dose ($p < 0·001$ for both) to values within the secretory phase range.

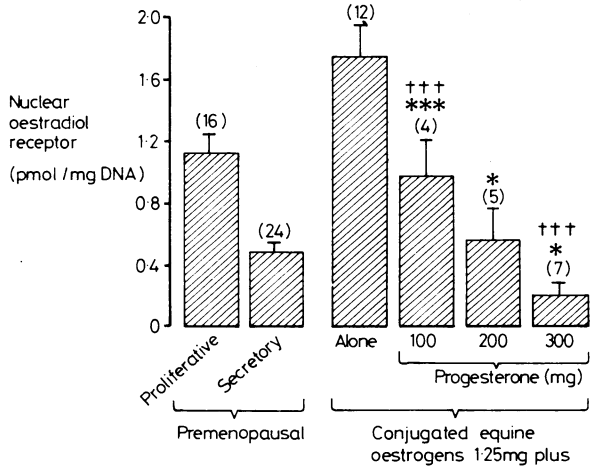


FIG 2—Nuclear oestradiol receptor in endometrium of postmenopausal women treated with conjugated equine oestrogens 1·25 mg daily continuously either alone or with progesterone 100 mg, 200 mg, or 300 mg daily added for 10 days each month. Proliferative and secretory phase ranges included for comparison. Results expressed as means and SEM. Numbers of observations given in parentheses. See fig 1 for key to p values.

*Conversion: SI to traditional units*—Nuclear oestradiol receptor: 1 pmol/mg DNA ≈ 272 pg/mg DNA.

## Discussion

From a comparison with the conjugated oestrogen only data it was clear that oral progesterone caused morphological and biochemical changes within the oestrogenised postmenopausal endometrium which were dose dependent.

Light microscopical changes correlated well with those seen under the transmission electron microscope and similar dose response relations were apparent. Progesterone 100 mg produced secretory changes in only five of 11 samples (45%) and failed to induce giant mitochondria and nucleolar channel systems. The combined score was only 25% (8/32). Hyperplastic features were seen in three specimens and it is tempting to speculate that the hyperplasia arose entirely because of an inadequate daily dose. This may not be true because it is now known that 12 days of administration of synthetic progestins is necessary for the

total suppression of hyperplasia in women receiving continuous oestrogen treatment,[8] and we prescribed oral progesterone for only 10 days each month. In our opinion, however, the 100 mg dose is too low for use in postmenopausal women taking exogenous oestrogens. Similar comments apply to the 200 mg dose, which caused secretory transformation in 10 of 13 samples (77%). In nine of these 10 specimens, however, a mixed endometrial pattern was observed, secretory features coexisting with proliferative and non-secretory type glands. Giant mitochondria were observed in six but nucleolar channel systems were seen in only two of the 11 specimens, and the combined score was 59% (27/46).

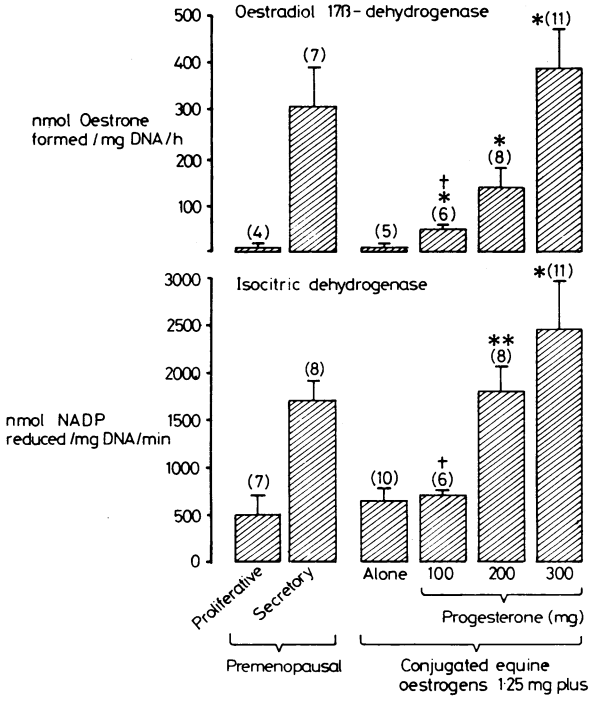


FIG 3—Activities of oestradiol-17β and isocitric dehydrogenases in endometrium of postmenopausal women treated with conjugated equine oestrogens 1·25 mg daily continuously either alone or with progesterone 100 mg, 200 mg, or 300 mg daily added for 10 days each month. Proliferative and secretory phase ranges included for comparison. Results expressed as means and SEM. Numbers of observations given in parentheses. See fig 1 for key to p values.

NADP=Nicotinamide adenine dinucleotide phosphate.

*Conversion: SI to traditional units*—Oestrone: 1 nmol ≈ 0·3 μg. NADP: 1 nmol ≈ 0·7 μg.

Progesterone 300 mg produced the best effects, with 10 of the 12 samples (83%) showing secretory transformation. Subnuclear accumulations of glycogen were seen in 11 samples (91%), but giant mitochondria were observed in only eight and nucleolar channel systems in only six of these samples, giving a combined score of 73% (35/48). Why the ultrastructural responses lacked the degree of uniformity observed with endogenous progesterone which achieved maximum effects in every specimen examined (100%; 32/32) is unclear. In addition, they compared less favourably with the synthetic progestogens norethisterone 2·5 mg and DL-norgestrel 150 μg, for which we have reported combined scores of 96% and 90%, respectively.[5]

The biochemical effects of oral progesterone were similarly dose dependent. Suppression of DNA synthesis and nuclear oestradiol receptor, which provide an index of antioestrogenic effects of oral progesterone, and induction of enzymatic activity, which assesses the secretory effects, were clearly suboptimal with the 100 mg dose. Values comparable to the premenopausal secretory phase range were induced by progesterone 300 mg. Intermediate effects were observed with the 200 mg dose.

Reasons for the discrepancy between the morphological and biochemical responses to progesterone 300 mg are unclear. With the androgenic progestogens norethisterone and DL-norgestrel we have reported a close correlation between the morphological and biochemical effects.[5,6] Thus, although oral progesterone undoubtedly exerts an end organ effect within the endometrium, the inability of 300 mg to induce uniform secretory and fine structural features suggests that larger doses may be required. Potential disadvantages to increasing the dose further include the development of adverse physical and psychological effects, whereas a potential advantage might be in increasing the efficiency of regular endometrial shedding. The latter is currently believed to be important in protecting against endometrial hyperplasia and is manifested by bleeding per vaginam.

Physical and psychological side effects and the patterns of bleeding per vaginam due to oral progesterone were recorded in this study and these data will be published in detail separately. In summary, the incidence of the commonest side effect, of a premenstrual tension like syndrome, was not dose dependent, being reported by 13% of patients taking 100 mg and by 17% of patients taking 300 mg. Only 43% of patients taking 100 mg experienced withdrawal bleeding after progesterone administration, and the lack of endometrial shedding on a regular monthly basis may help explain the development of endometrial hyperplasia in three patients within this group, the retained endometrium being subjected to a chronic oestrogenic stimulus. With 300 mg, 77% of patients experienced regular withdrawal bleeding. Thus larger doses are unlikely, in our opinion, to increase the incidence of physical or psychological side effects, or both, but may effect more efficient endometrial shedding.

We believe that because oral progesterone does not cause gross adverse metabolic effects,[21,22] its use as an alternative to synthetic progestogens for addition to postmenopausal oestrogen treatment warrants further evaluation. It may also have a role in the management of other progestogen responsive conditions such as dysfunctional uterine bleeding and might be usefully combined with synthetic oestrogen in oral contraceptive treatment.

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# Propranolol as a novel, effective spermicide: preliminary findings

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## Abstract

**The efficacy and tolerability of 80 mg propranolol tablets as a vaginal contraceptive were studied in 198 fertile women for 11 months. The calculated one year life table pregnancy rate was 3·4/100 women and the Pearl index was 3·9/100 women years. No major adverse effects were encountered.**

**The findings suggested that propranolol is an effective vaginal contraceptive whose failure rate compares favourably with that of other methods of contraception. Further study of propranolol and similar compounds is warranted.**

## Introduction

Spermicides are biologically an obvious way of interrupting human fertility and should be convenient to use. The contribution of vaginal spermicides to contraception is becoming more widespread[1] but there has been a reduction in the number of products available over the past two decades.[2] Advantages of spermicides include safety, availability, simplicity, convenience, and acceptability. In addition, they are appropriate for short term use or for use in conjunction with other methods. Unfortunately, however, their failure rate compared with other forms of contraception and the need to apply them shortly before intercourse limit their use and usefulness. Hence there is a need to develop novel, effective agents as spermicidal contraceptives.

Nonoxynol 9 is the active ingredient most widely used in spermicides. Chvapil *et al* reported liver toxicity in animals when nonoxynol 9 was injected intraperitoneally.[3] Some investigators found that women who received nonoxynol 9 per vaginam for 14 days had a reduction in their serum cholesterol concentration but no changes in other values reflecting liver function.[4] In another study in women with a smaller dose of nonoxynol 9 applied per vaginam, however, these findings were disputed.[5] Currently no analytical method is available to identify and quantify nonoxynol 9 in human tissues, although studies in rabbits with $^{14}$C-nonoxynol 9 indicate that it is extensively absorbed from the vagina.[3]

Quinine, the dextro isomer of quinidine, has long been used in Europe as a vaginal spermicide, albeit a rather ineffective one.[6] In 1973 propranolol, chlorpromazine, phenoxybenzamine, and other drugs were reported to inhibit the motility of spermatozoa in vitro.[7] The property common to these drugs is membrane stabilising activity. Both the racemic dextrolaevo mixture and the dextro isomer of propranolol were shown to inhibit sperm motility.[7] This suggests that the effect on sperm motility is independent of beta receptor blockade, since D-propranolol has only very weak beta receptor blocking properties. Although membrane stabilising activity has in the past been used synonymously with local anaesthetic activity, it is apparent that there is a

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