A NEW TYPE OF ORAL CONTRACEPTIVE

BY

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The Council for the Investigation of Fertility Control has just approved a fourth oral contraceptive tablet, "volidan," containing 4 mg. of megestrol acetate with 0.05 mg. ethinyloestradiol (EE). The progestogen in the product, megestrol acetate, is 17 α -acetoxy-6-methyl-6-dehydropregesterone, a new compound synthesized in the laboratories of the British Drug Houses (Petrow *et al.*, 1960; Petrow, 1963).

Earlier progestogens used for ovulation-inhibition (norethynodrel and norethisterone acetate) are 19-nor steroids which are metabolized in the body to oestrogens (Brown and Blair, 1960; Paulsen *et al.*, 1962). Megestrol is a derivative of progesterone and does not appear to undergo metabolic transformation to oestrogen.

Preliminary laboratory studies (Elton *et al.*, 1960; David *et al.*, 1963) had shown this compound to be one of the most active of the known anti-ovulatory and progestational agents—for example, in rabbits a single dose of 0.05 mg./kg. completely prevented ovulation in 20 animals, and in the Clauberg assay 5 μ g./kg. given daily for four days gave a McPhail score of 2.5. This compound showed no androgenic activity, and no oestrogenic properties could be detected by the Alan Doisy or Lauson assays. Prolonged administration to rats produced no apparent adverse effects on the fertility of male or female rats and no virilizing effect on the developing foetus. It had no systemic anti-inflammatory glucocorticoid properties or effect on water and electrolyte excretion.

Preliminary Clinical Assessment

When clinical studies were begun in March, 1960, it seemed that 2 mg. would be an adequate dose; at this dose Swyer and Little (1962) found inhibition of ovulation as shown by pregnanediol excretion studies in all of eight cycles. The postponement of menstruation assay (Swyer and Little, 1962) indicated that megestrol acetate had an ED₅₀ of 1.8 mg. when combined with oestrogen, and the endometrial progestational response showed a good balance of glandular and stromal development more like a physiological response than had been found with the 19-nor steroids.

In the first place, therefore, 25 volunteer patients were given this product in a dosage of 2 mg. megestrol

acetate + 0.05 mg. ethinyloestradiol, and they were followed for 278 cycles. As can be seen from Tables I, II, and III, though this proved to be an effective dose it was unsatisfactory, as it gave 32% of breakthrough bleeding in the first cycle and 29% of breakthrough bleeding in all cycles. It seemed, therefore, that a number of different tablet strengths and proportions of the progestogen/oestrogen should be tried, and a number of tablet formulations were made and trials on a larger scale initiated.

Organization of the Trial

Full details of the organization of trials under C.I.F.C. have been given (Mears, 1961; Eckstein *et al.*, 1961; Mears and Grant, 1962; Pullen, 1962). The women were all under 40 and had proved their fertility. Routine cancer smears were taken before medication in all cases, also a full medical and menstrual history. A number of volunteers on each dosage enrolled in the Central Office Trial also had routine endometrial biopsies and vaginal and cervical smears. Routine Papanicolaou smears taken before the trial began revealed one suspicious positive smear, and this woman was referred for investigation and treatment (hysterectomy) and was not included in the trial.

Effectiveness as an Oral Contraceptive

In 183 women who have taken various doses of volidan for a total of 1,457 months it has effectively prevented pregnancy where tablets have been taken as instructed (Table I). In addition, patients have missed one or two tablets in 70 cycles without any pregnancy occurring. Pregnancy did occur in two cases in which

TABLE I.—Effectiveness

No. of Patients	No. of Cycles Completed	Pregnancies		No. of Cycles in which Tablets Missed
		Tablets Failure	Patient Failure	
183	1,457	Nil	2	70

the tablets were wrongly taken; one was a patient who had for seven months effectively taken 2 mg. megestrol acetate + 0.05 mg. EE tablets. Because of persistent breakthrough bleeding the dosage was doubled by taking two tablets a day. This dosage produced a recurrence of the nausea which she had found in the first cycles, and as she was going on holiday the next month she reduced the dosage to one tablet a day and became pregnant. This suggests that although 2 mg. + 0.05 mg. EE is adequate to control conception it is a borderline dose; it also suggests that the dose of an oral contraceptive should not be reduced when the patient is stabilized on one dosage. The other patient, a Nigerian, vomited up most of the tablets for the first month but did not mention this until pregnancy was suspected.

Side-effects

In order to be able to compare the results using different oral contraceptives, all side-effects recorded by the patient in her chart are noted and analysed, and are here reproduced for the sake of comparison with similar products. However, these figures do not show the large numbers of women under medication who are relieved of dysmenorrhoea, premenstrual tension, breast discomfort, headache, tiredness, and depression. The

figures show only those who have recorded these symptoms—in fact, most of them complained of these same symptoms before medication—and doctors should not be misled by their seemingly high incidence; very few patients had any even of their original complaints after 12 cycles.

The side-effect of most importance to the patient at the beginning of medication is nausea in the first cycle, and four patients in fact withdrew from these trials because of severe nausea; but all these patients were having tablets containing 0.1 mg. EE. As can be seen from Table II, this dosage of oestrogen gives a much bigger incidence of nausea than the tablets containing 0.05 mg. (no patients withdrew because of nausea with this dose). This shows an interesting difference between

TABLE II.—*Side-effects. Percentage of Cycles*

Tablet:	2 mg. + 0.05 EE	2 mg. + 0.1 EE	3 mg. + 0.1 EE	4 mg. + 0.05 EE	4 mg. + 0.1 EE	5 mg. + 0.1 EE	5 mg. + 0.1 EE3ME
No. woman/ months	26/278	25/127	111/676	24/114	27/104	36/55	36/103
Nausea:							
1st cycle	50%	40%	11%	7%	37%	34%	34%
All cycles	8%	22%	16%	6%	17%	30%	25%
Breast discom- fort:							
1st cycle	39%	16%	12%	20%	7%	16%	33%
All cycles	10%	11%	5%	20%	3%	11%	21%
Headaches:							
1st cycle	8%	24%	10%	12%	32%	14%	12%
All cycles	10%	10%	8%	7%	10%	10%	9%
Tiredness and depression	5%	Nil	3%	10%	Nil	2%	5%
Change in weight (3 lb. (1.36 kg.) or more)	+14%	48%	28%	8%	29%	50%	30%
	-10%	0	9%	12%	Nil	2%	8%

the use of ethinyl oestradiol in oral contraception and ethinyl oestradiol 3-methyl ether, in which the incidence of nausea is not related to the dose (Mears, 1963). There is also some increase in weight of 3 lb. (1.36 kg.) or more in about one-quarter of all patients. This again appears to be significantly greater in tablets with the higher dosage of oestrogen.

Cycle Control

From the physician's point of view cycle control is the most important factor in assessing the optimum dose and proportion of oestrogen, and it can be seen from Table III how varied the results are. When the incidence of breakthrough bleeding with 2 mg. megestrol acetate + 0.05 mg. EE was found to be so high (29% over all cycles), these patients were all switched to a dose of

TABLE III.—*Cycle Control. Percentage of Cycles*

Tablet:	2 mg. + 0.05 EE	2 mg. + 0.1 EE	3 mg. + 0.1 EE	4 mg. + 0.05 EE	4 mg. + 0.1 EE	5 mg. + 0.1 EE	5 mg. + 0.1 EE3ME
B.T.B.:							
1st cycle	32%	16%	16%	8%	12%	3%	3%
All cycles	29%	12%	16%	6%	6%	10%	1%
Spotting	15%	15%	8%	6%	7%	14%	1%
Amenorrhoea	3%	2%	1%	1%	Nil	Nil	2%
Change in flow	+2%	4%	8%	3%	Nil	10%	2%
	-20%	50%	16%	55%	27%	20%	21%

3 mg. + 0.1 mg. EE. The lowest incidence of breakthrough bleeding was eventually found with 4 mg. megestrol acetate + 0.05 mg. EE.

The incidence of amenorrhoea is similar to that observed with other available oral contraceptives.

A small number of patients have an increased menstrual flow, and these have all been associated with recurrent breakthrough bleeding. As with other oral contraceptives, therefore, there are a few patients whom the progestogen does not suit and who should be changed on to an oral contraceptive containing a different progestogen. A considerable proportion of patients on each tablet strength have a decreased amount of flow, though clinically this decrease in flow appears to be less marked than with the other available oral contraceptives.

The dose chosen as the optimum to be marketed as volidan (4 mg. megestrol + 0.05 mg. EE) gives an overall incidence of 6% breakthrough bleeding, with 1% amenorrhoea; in 55% of patients there was some decrease in the amount of menstrual flow.

Acceptability

The acceptability of volidan, as with other contraceptives, has been high in this trial, though it should be remembered that patients volunteering to take part in our trials tend to be highly fertile, have had previous difficulty in controlling their fertility, or are tired of mechanical methods. These patients are much relieved to find oral contraception effective and to be able to avoid using conventional methods. The number of withdrawals from the trial is given in Table IV and the reasons for withdrawal are analysed in Table V; 34 patients withdrew for reasons connected with the method, and 11 for other reasons, such as a desire for pregnancy or leaving the district.

TABLE IV.—*Number of Withdrawals*

	2 mg. + 0.05 EE	2 mg. + 0.1 EE	3 mg. + 0.1 EE	4 mg. + 0.05 EE	4 mg. + 0.1 EE	5 mg. + 0.1 EE	5 mg. + 0.1 EE3ME
No. withdrawn	10	2	23	5	Nil	1	4

TABLE V.—*Reasons for Withdrawal*

Dosage	Reasons Connected with the Method						Reasons Not Connected with the Method		
	Nausea	Headache	Depression	Irreg. Cycles	Other Reasons	Total	For Pregnancy	Others	Total
2 mg. + 0.05 EE ..		3		1	1	5	2	3	5
2 " + 0.1 EE ..				1	1	2			
3 " + 0.1 EE ..	4		3	6	5	18	2	3	5
4 " + 0.05 EE ..		1		1	3	5			
4 " + 0.1 EE ..	Nil		1			1		Nil	
5 " + 0.1 EE ..				1	1	2			
5 " + 0.1 EE3ME		1				1	1		1
Total No. ..						34			11

Assessing the Optimum Dose

This was the first of the newer progestogens to be given to C.I.F.C. to study from the earliest stages: previous products had already received a considerable amount of clinical study and the optimum dose had been established before they were used in this country.

This trial shows our method of assessing the optimum dose through the study of a minimum of 25 patients on each of several doses and proportions of oestrogen. This is a time-consuming method, as the patients have

to be studied for some months and the clinical results evaluated. From a clinical point of view the most important criteria would appear to be a low incidence of nausea in the first cycle, with breakthrough bleeding as low as possible and certainly occurring in less than 10% of cycles. Much less nausea and a smaller increase in weight occurred in the groups given 0.05 mg. oestrogen than in those given 0.1 mg. EE, and the lowest incidence of breakthrough bleeding (6%) was found with a combination of 4 mg. megestrol acetate + 0.05 mg. EE (volidan).

Attempts are now being made to find a less time-consuming method of assessing dosage—for example, attempted correlation with endometrial biopsies and cytological smears; so far these have not yielded anything useful.

Endometrial Biopsies

Preliminary studies show that, as with other oral contraceptive products, neither glands, vessels, nor stroma present the normal physiological cyclic pattern.

There appears to be a short, very modified secretory phase extending over a week from the seventh day onward. There is very little glandular growth, and only the presence of subnuclear vacuoles indicates the abortive secretory phase. Stromal oedema is present during this period and the vessels are prominent. Following this there is regression of glands, which become small and straight, with basal nuclei and no mitoses. Stroma is dense and the vessels inconspicuous.

At no stage in the cycle do the glands show the enlargement, tortuosity, or scalloping seen in the normal secretory endometrium, although the glands appear to be larger and there is a more normal balance between glandular stromal development than is found in the endometrium of patients on 19-nor compounds.

Vaginal and Cervical Cytology

In none of these vaginal or cervical smears examined was there the slightest evidence of any cellular or nuclear variation from normal. No definite pattern of hormonal change has yet emerged and there appears to be less reduction in oestrogenic effect as shown by the cornification index than has been found with oral contraceptive tablets containing norethynodrel and norethisterone. This confirms the findings of Jackson (1962).

Long-term Effects

As usual, a minimum of 100 patients will be kept on volidan tablets indefinitely for long-term study. There have been no cases of thrombophlebitis among patients taking part in this trial. There have been no positive cancer smears after medication, although, as already stated, one was found before medication and the patient was consequently excluded from the trial.

Summary

Clinical trials of a new oral contraceptive, volidan (4 mg. megestrol acetate + 0.05 mg. EE), have been carried out under the auspices of the Council for the Investigation of Fertility Control.

Megestrol acetate proved to be effective in doses of 2 mg. and upwards and there were no pregnancies in

183 patients receiving medication for 1,457 cycles where the tablets were taken as instructed.

Although previous laboratory and clinical tests suggested that 2 mg. megestrol acetate + 0.05 EE would be an adequate dose—and it was indeed effective—this did not produce good enough cycle control: optimum cycle control was obtained with 4 mg. megestrol acetate + 0.05 mg. EE, which is to be made available commercially as volidan.

Cycle control with this dosage was excellent, with an incidence of breakthrough bleeding of 6% over all cycles and of 1% amenorrhoea, with a small decrease in menstrual flow in 55% of patients. The incidence of nausea in the first cycle was only 7%.

Volidan differs from the earlier 19-nor steroid oral contraceptives which possess inherent oestrogenic activity in that it produces a more normal type of endometrium and does not depress the vaginal cornification index so much.

I wish to acknowledge grateful thanks to Dr. Ellen Grant, of Barnet and Central Office Clinics, and Dr. S. Cochrane, of the Westminster Clinic, for medical care of patients taking part in this trial and for the painstaking way in which they recorded and sent in results and helped in preparing these for this paper; also to Dr. Mary Egerton and Dr. A. W. Kirshner, who have done all the cytological smears for patients taking part, and to Dr. Kirshner for pathological reports on the endometrial biopsies. I am also grateful to the British Drug Houses Limited for supplies of all the tablet formulations mentioned.

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With the conclusion of the building operations at the Ciba Foundation the Hunterian Society's library and museum is once again able to function normally. Among the many acquisitions during the year pride of place must be given to the recent gift of Mr. Patrick Hunter Jobson, Honorary Fellow of the Society and senior male representative in the Hunterian descent, of three folio volumes of letters, known far and wide as the Hunter-Baillie MSS, of which another nine volumes of the same series were presented some 50 years ago to the Royal College of Surgeons by the late Miss Helen Hunter Baillie, the present donor's aunt. The contents of the gift, comprising some thousand or so letters and MSS dated from the 17th to the 20th centuries, have been handsomely rebound by the British Museum, and considerable progress has been made in describing and annotating them for future reference. The task, however, is a considerable one, and several months may elapse before the volumes will be available for general inspection. (Curator's Report, Library and Museum, Hunterian Society.)