ventilated areas than oxygen which was taken as a single breath. Comparisons of blood flow were made by injecting intravenously xenon dissolved in saline and observing the amounts evolved into different regions of the lungs.

Xenon proved of particular value in studies of poorly ventilated regions of the lung because less information was available about their function from studies with radioactive oxygen. For most other purposes the two methods gave similar results, although xenon was useless for detecting left-to-right shunts, for which carbon dioxide labelled with $^{15}\text{O}_2$ is of particular value. Furthermore, C^{15}O_2 can be used to compare flow rate and changes in it but xenon can only be used to determine the relative flow through two areas. Normal subjects had a low blood flow through the upper zones of their lungs and, in contrast, patients with severe mitral stenosis had a high upper-zone blood flow with a very limited flow in the lower zones. Both methods sometimes revealed striking regional ventilation abnormalities which were not apparent on chest radiographs.

The main practical advantage of xenon lies in its longer half-life (5.4 days) against the very short one (two minutes) of $^{15}\text{O}_2$. Although $^{15}\text{O}_2$ is more versatile for research purposes its short half-life makes its general use impracticable. Xenon-133 is generally available and could be widely applied in thoracic centres for evaluation of patients before lung surgery and for physiological and clinical investigation of patients with regional disease of the lungs.

We thank Mr. G. Forse for valuable technical assistance and the operators and engineers of the M.R.C. cyclotron for the production of the $^{15}\text{O}_2$. We are grateful to Mr. D. Vonberg, Dr. J. F. Fowler, and Professor J. McMichael for their interest and support.

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"CONOVID-E" AS AN ORAL CONTRACEPTIVE

BY

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In August, 1960, a clinical trial of "conovid-E" (2.5 mg. norethynodrel with 0.1 mg. ethinylloestradiol-3-methyl ether) was begun at the Slough and District Family Planning Clinic, under the auspices of the Council for the Investigation of Fertility Control. The object was to ascertain the efficiency of this small dose of norethynodrel in conjunction with 0.1 mg. of ethinylloestradiol-3-methyl ether. After publication of the results of the Birmingham oral contraceptive trial (Mears, 1962), a comparison could be made of the incidence of side-effects produced by the 2.5-mg. dosage with those given by conovid (5 mg. norethynodrel with 0.075 mg. ethinylloestradiol-3-methyl ether).

When the first 200 patients were reviewed in December, 1961, 162 were still taking part in the trial. The reasons given by the patients for leaving the trial are shown in Table I.

TABLE I.—Reasons for Leaving Trial

Dissociated from Oral Contraceptive	Indeterminate	Associated with Oral Contraceptive
Left the area .. 5	"Changed mind" 7	"Felt ill" .. 7
To become pregnant 3	Developed a cervical erosion 1	Nausea in 1st cycle .. 4
Transferred to separate post-partum trial .. 2	Developed a cervical polyp .. 1	Short cycles .. 2
Entered hospital for vaginal repair 1	Entered hospital for cautery of erosion .. 1	Heavy periods .. 1
Under hormone treatment elsewhere .. 1		Pregnant, owing to intermittent dosage .. 2
Total .. 12	Total .. 10	Total .. 16

TABLE II

Cycles	1	2	3	4	5	6	7, 8, 9	10, 11, 12	12+
No. of women-months ..	183	175	154	121	116	84	162	77	42

The results now given are based on 1,114 woman-months, made up as shown in Table II. The greatest number of cycles completed by any one patient during the time of review is 18.

Selection of Patients

Volunteers were married women, under 40 years on entry to the trial, with at least one living child. The youngest patient was aged 18. Lactating women were not accepted. In every case the written consent of the husband was obtained before the wife was accepted into the trial.

Of the volunteers, 47.5% had not sought contraceptive advice at a family planning clinic before. Either they had not wished to limit their families previously or, more probably, they rejected the idea of conventional mechanical methods. Some, though not wanting to have another child, had either disliked or been casual with mechanical methods, and consequently had a high failure rate.

Although in apparent normal health on their first examination they gave histories of numerous common disorders, and, in addition, the following:

Gynaecological: Removal of ovary; removal of ovarian cysts; removal of fibroids; endometriosis.

Infections: Tuberculous meningitis; pulmonary tuberculosis; tuberculosis of spine; bronchiectasis (pneumonec-tomy); rheumatic fever; osteomyelitis; catarrhal jaundice.

Others: Thyrotoxicosis; hypertension; "kidney trouble"; asthma; colitis; gall-stones; psoriasis; gastric ulcer; duodenal ulcer; anxiety neurosis; endogenous depression.

Organization of the Trial

This was similar to those already described elsewhere (Eckstein *et al.*, 1961; Mears, 1961; Mears and Grant, 1962). The relationship between the general practitioners, the consultants, and the clinic was very good. The general practitioner was notified when his patient wished to volunteer, and all co-operated fully.

The routine of the administration of the tablets did, however, differ from those of previous trials. Beginning on the fifth day of a menstrual cycle, one conovid-E tablet was taken nightly 21 times. The tablets were then stopped for seven days, during which time withdrawal bleeding usually occurred. If ever this did not take place the patient was told emphatically to start the next course of 21 tablets after seven days without. In the event of "spotting" before the course of tablets was finished, the patient was told to record it on her chart and to complete the course. If bleeding as heavy as a normal period took place before the completion of a course the tablets should be stopped and five days, instead of seven days, should be allowed free of tablets. In this way it was hoped to control "spotting" and breakthrough bleeding, and, indeed, in numerous patients this result was achieved after three or four cycles.

No other contraceptive measures were advised and no pregnancies resulted from this policy. However, in view of the fact that 0.1% of women may ovulate very early in a cycle (Latz and Reiner, 1942), it has since been recommended that the tablets should not be relied upon during the first week of the first cycle only.

Efficiency of Tablets.—No pregnancies have occurred among patients taking the tablets regularly or those who have missed occasional tablets. Only two pregnancies have resulted; one patient did not start the tablets until the 15th day of the 13th cycle, and a second took three tablets, and then missed six tablets before taking seven more.

Menstrual History Before the Trial.—Normal healthy women are said to have a shortened cycle of less than 24 days in over 10% of cycles (Haman, 1942). When questioned on cycle length at their first examination the volunteers tended to give what they believed to be the acceptable answer—that is, 28 days. None had kept a detailed record and most relied on memory. Four per cent. gave histories of regular cycles of 24 days or less. On the other hand, 19.5% recounted cycles of 30 days or more, either regularly or irregularly. As these were patients anxious not to become pregnant, it is not surprising that they were acutely aware of cycles prolonged beyond their "normal," while short cycles passed unnoticed by them.

Cycle Control During the Trial

Amenorrhoea.—After the tablets had been started four patients did not bleed at the end of the first cycle. The incidence of amenorrhoea is shown in Table III.

TABLE III.—Incidence of Amenorrhoea

	1st Cycle	2nd Cycle	3rd Cycle	6th Cycle	Other Cycles
2.5 mg.	2.5%	Nil	Nil	6%	10%

Though the number of patients affected is small, all patients should be warned that a period may occasionally be missed. This effect causes more alarm and anxiety than any other.

Breakthrough Bleeding and Spotting

Breakthrough bleeding is defined as bleeding as heavy as a normal period when it occurs before the course of tablets has been completed. A comparison with the 5-mg. tablet is shown in Table IV.

TABLE IV.—Incidence of Breakthrough Bleeding

	1st Cycle	2nd Cycle	3rd Cycle	6th Cycle	Other Cycles
2.5 mg.	31%	28%	19%	29%	27.5%
5 "	23%	26%	18%	13%	16%

Breakthrough bleeding was more troublesome technically than in practice. With two exceptions the patients did not mind short cycles; on the contrary, they welcomed the recurring evidence that they were not pregnant. However, it was thought to be undesirable that bleeding should occur too frequently, and eight patients were transferred to the 5-mg. tablet after having had from three to eight cycles with breakthrough bleeding. This increased dose of norethynodrel (but decreased dose of ethinyloestradiol-3-methyl ether) controlled the bleeding in three patients, but the remainder continued to break through. Of these five, two were transferred after a further five cycles to the 10-mg. dose (with 0.15 mg. of ethinyloestradiol-3-methyl ether), which still did not prevent breakthrough bleeding.

It was then decided to try the effect of 1½ tablets of the 2.5-mg. dose—that is, giving 3.75 mg. of norethynodrel with 0.15 mg. of ethinyloestradiol-3-methyl ether, through the cycle. In 13 patients who had had breakthrough bleeding and spotting during 3 to 13 cycles on the 2.5-mg. tablets, greatly improved cycle control resulted: 11 were then controlled, but one could not tolerate an increase in nausea, and two were still breaking through after three cycles on this increased dosage. It would seem that 0.15 mg. of the oestrogen compound controlled the breakthrough bleeding better when combined with 3.75 mg. of norethynodrel than when combined with 10 mg. of norethynodrel.

In the trial as a whole, 52% of the patients had a decreased menstrual loss, and 8% noticed an increased amount.

Side-effects

The patients have been extremely enthusiastic about the method. With few exceptions even those who had experienced side-effects in the first few cycles have been sufficiently well pleased with the method to persevere.

Nausea.—As in other trials the side-effect that the patients found most trying was nausea, especially if accompanied by lethargy and a disinterest in life. It

was not found to be helpful to divide the symptom of nausea into slight, moderate, and severe degrees, as the assessment was such a subjective one. Whatever the degree, as estimated by the patient, it had cleared considerably by the second cycle, and all were free of it by the fourth cycle. In no case was an anti-emetic or antihistamine given. The incidents of nausea after the third cycle were probably of infective origin and dissociated from the tablets. No correlation was found between those who experience nausea and vomiting in pregnancy and those who had this symptom as a side-effect. Though not necessarily nauseated, some preferred to give up smoking while on the tablets. Table V shows the incidence of nausea and of nausea with vomiting (Mears, 1962). The main factor which appeared to influence those not dropping out of the trial because of this symptom was the confidence that the patient had in the medical staff.

Breast Discomfort.—Table VI shows the number of patients who noticed breast discomfort, particularly premenstrually, while taking the 2.5- or 5-mg. tablets (Mears, 1962). Unfortunately the first 60 patients were not specifically asked at their first examination whether

TABLE V

	1st Cycle	2nd Cycle	3rd Cycle	6th Cycle
<i>Nausea</i>				
2.5 mg.	46%	16%	2.4%	3%
5 "	36%	14%	9%	6%
<i>Nausea with Vomiting</i>				
2.5 mg.	6%	4%	Nil	Nil
5 "	6%	5%	4%	1%

TABLE VI

	1st Cycle	2nd Cycle	3rd Cycle	6th Cycle	Other Cycles
2.5 mg.	21%	16%	4%	11%	1%
5 "	24%	17%	12%	14%	15%

or not they had premenstrual breast tenderness. On questioning the remaining 140 volunteers, this information was obtained: 16 patients had premenstrual breast tenderness before and after taking conovid-E; 11 had premenstrual breast tenderness before but not after taking conovid-E; and 14 did not have premenstrual breast tenderness before, but did so after taking conovid-E. In some there was an increase in size without discomfort. Those who considered themselves too thin were delighted with this change.

Dysmenorrhoea.—As with the symptom of nausea, it was difficult to judge degrees of dysmenorrhoea. Initially many women said they had none, yet after taking a course of tablets they remarked that the bleeding was quite free of pain. When the discrepancy between their accounts was brought to their notice they tended to modify their original statements by saying that they had no more pain "than was normally expected." Obviously, to many a slight degree of dysmenorrhoea was "normal." Of the 59 patients who complained of dysmenorrhoea before entering the trial, 14% noted no change before and after taking the tablets, 19% had an increase in pain in some cycles only, and 67% had a decrease in pain. Anovulatory cycles are said to be free of dysmenorrhoea, so another mechanism, probably the amount of progestational steroid, must be responsible for this symptom when ovulation is inhibited. Table VII shows the comparison of dysmenorrhoea with the different strength of tablets (Mears, 1961).

Weight Changes.—There appeared to be no consistent trend in weight changes. At the end of six months 28% had gained 3 lb. (1.4 kg.) or more and 17% had lost 3 lb. (1.4 kg.) or more. Only one patient gained more than a stone (6.4 kg.) by the end of 18 cycles. Her height was 5 ft. 6 in. (167.5 cm.). On entering the trial her physical condition was poor, and her anxiety to avoid another pregnancy made her almost suicidal. Her increase in weight to 10 stone (63.5 kg.) merely paralleled that of her well-being in every other respect.

Premenstrual Tension.—Similarly the effect of the hormones was variable on this syndrome. On direct questioning 81 patients said they had had symptoms of premenstrual tension before taking the tablets. In 20 the symptoms were unchanged; 53 patients noticed an improvement, and of these 36 were pleased that they were completely free of these symptoms. The tension was increased, however, in three patients and five developed tension who had previously not had it. Table VIII shows that premenstrual tension tended to decrease with longer medication (Mears, 1962).

TABLE VII

	1st Cycle	2nd Cycle	3rd Cycle	6th Cycle	12th Cycle	Later Cycles
2.5 mg.	2%	2%	1%	2%	3%	3%
5 "	11%	23%	11%	6%	3%	Nil

TABLE VIII

	1st Cycle	2nd Cycle	3rd Cycle	6th Cycle	12th Cycle	Other Cycles
2.5 mg.	6%	3%	6%	Nil	3%	Nil
5 "	4%	3%	3%	2%	Nil	Nil

Cervical Erosions.—The cervix was examined initially, and at six-monthly intervals unless any symptom indicated that it should be reviewed sooner. Twenty-four patients had erosions before starting the tablets, and in four the lesion was stationary for as long as 17 cycles later. The remainder cleared during but not necessarily because of the therapy. During the first five cycles of treatment seven patients developed erosions, and one of these required cautery. No new erosions occurred after the fifth cycle in any patient. One patient was found to have a cervical polyp in the second cycle; this was removed in hospital. No carcinomatous changes were detected clinically in any patient.

Other Side-effects.—Only isolated incidences of abdominal cramp and increased or decreased vaginal discharge have occurred, and these have not been a clinical problem. Headaches and dizziness have not worried the patients unduly as with some other oral contraceptives. No cases of acne were seen, and premenstrual spottiness tended to clear. One patient developed two patches of alopecia. At the time of the review (December, 1961) the skin of the patient with psoriasis had not cleared as this condition sometimes does in pregnancy; however, by May, 1962, the lesions were no longer visible. Several patients slept more deeply. An attempt was made to try to correlate the likelihood of side-effects happening in any given patient, but no indication could be found either in the past history or in the medical or gynaecological examinations.

Discussion

Many nationalities, the five social grades, and all levels of intelligence were represented in the trial. The

great majority had no difficulty in understanding and carrying out the method, and they kept their appointments and their charts very well. Though numerous patients missed occasional tablets, the majority of tablets were taken regularly and conscientiously. The routine of pill-taking became automatic. As one patient remarked, "the beauty of the pill is that you can forget it."

However, it must be realized that the women in the trial were selected in that, for various reasons, they did not favour mechanical contraception. Therefore it was to be expected that they would be favourably inclined towards an entirely different method of birth control. Also the tablets, supplied by G. D. Searle & Co. Ltd., were issued free to the patients.

Numerous cases of marital difficulties were encountered, and in some, no doubt, these problems prompted the patients to enter the trial. Most were improved as a result of so doing, but many more complex factors must have been involved than the mere taking of a pill. The overall effect, however, was that the patients felt an increase in well-being and marital happiness. The effects were not limited to the wives. Many husbands expressed their satisfaction with the method and none wished to return to methods formerly used. One man was almost impotent and returned to full potency, but it would be unwise to draw conclusions from a single case.

None of the marital problems became worse, but in those cases where there was no improvement there was a deepening sense of disappointment. It remains to be seen whether these patients will eventually give up oral contraception. To date, they have chosen to continue, despite the fact that it is not the panacea for their marital ills as they anticipated.

Those patients who had left the trial to become pregnant conceived in the cycle following the cessation of tablets. One patient miscarried at eight weeks, and one pregnancy continues normally. The third patient had a normal quick delivery of a healthy 8½-lb. (3.8-kg.) girl, and this was followed by an abundant lactation.

The minor disadvantages of oral contraceptives can readily be shown by tables. The contribution they make to human happiness does not lend itself to statistical analysis. The overall clinical impression is that conovid-E is psychologically and physically acceptable and its effects are reliably reversible over the time tested.

Summary

The object of the trial was to ascertain the smallest dose of norethynodrel combined with ethinylloestradiol-3-methyl ether that would be an efficient contraceptive.

After 17 months 162 women out of the first 200 fertile volunteers were still in the trial and information has been obtained from 1,114 woman-months of therapy.

The routine administration of 21 tablets, followed by seven days without tablets, is acceptable to the patients.

Menstrual-cycle control on a tablet of 2.5 mg. of norethynodrel with 0.1-mg. of ethinylloestradiol-3-methyl ether was unsatisfactory in 30% of women, but "spotting" and breakthrough bleeding were checked by increasing the dosage to one and a half tablets.

Nausea was the side-effect most often complained of, but this was limited to the first three cycles.

No pregnancies occurred when the tablets were taken as prescribed.

After cessation of the treatment, ovulation and fertility appeared to be unimpaired.

The trial continues.

It is concluded that a tablet of 2.5 mg. of norethynodrel with 0.1 mg. ethinylloestradiol-3-methyl ether gives full effective conception control. The patients were strongly in favour of oral contraception once they had used this method of birth control.

Dr. E. Mears and Dr. G. R. Venning have given great help in the organization of the trial (first run by Dr. G. Newbury) and in the preparation of this paper. Dr. A. Wiseman has willingly supplied additional data. The clerical work was ably carried out by Mrs. Anne Try. The trial would not have been possible without the willing co-operation of the volunteers.

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✓ DETERMINING THE CLIMATIC LIMITATIONS OF A CHILDREN'S CANCER COMMON IN AFRICA ✕

BY

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It has recently been recognized that a strikingly characteristic lymphoma syndrome is the commonest children's cancer across tropical Africa. The clinical and pathological features of the varying manifestations of this multifocal neoplasm have been described elsewhere (Burkitt, 1958, 1962a, 1962b; O'Connor and Davies, 1960; Burkitt and O'Connor, 1961; O'Connor, 1961; Burkitt and Davies, 1961).

One of the most fascinating aspects of this easily recognizable syndrome is its limited geographical distribution. The rough outline of the tumour-bearing belt across Africa (Fig. 1) has been described in the papers referred to above, and its obvious relationship to certain climatic factors has been stressed. Moreover, the marked similarity between tumour distribution and tsetse infestation has been noted.

Recently extensive travel has been undertaken to determine more accurately the limits of this "tumour belt" and the physical and climatic conditions determining the boundaries. These journeys have been made in order to provide what might well be termed "geographical biopsies"—that is, detailed surveys of portions of Africa containing "tumour-bearing" and "tumour-free" areas, analogous to the surgeon's biopsy in which the pathologist expects to find the change from normal to diseased tissue.

Tumour "Safaris"

In the past this East African term applied primarily to foot travel with porters. It is now used for journeys by almost any means, usually of more than a day's duration.