the possible need for later ventriculography, mean that the whole procedure should not be undertaken by one who is not sufficiently trained and experienced. The temptation to use subdural needling indiscriminately as part of a battery of tests must be firmly resisted.

It is essential at the first diagnostic aspiration to replace part of the removed fluid by air so that later *x*-ray films will serve to differentiate between the occasional case of gross hydrocephalus with very thin cortex, the porencephalic cyst lying near the anterior fontanelle, and the true subdural effusion. Such radiographs are also valuable in assessing the size of the effusion and hence judging whether repeated aspiration is likely to succeed in effecting a cure (see Fig.).

Treatment

Occasionally after successive aspirations the quantity of fluid diminishes rapidly, and subsequent radiographs after air replacement confirm that the subdural space is diminishing. Cure of the condition by aspiration is, however, uncommon, and is particularly unlikely in those babies who have had the fluid for more than a few weeks, so that a well-formed membrane is present. Sherwood (1930) introduced the idea of removing the subdural membrane by craniotomy, a technique which has been modified only in minor respects since it was first practised. The procedure can be formidable, and hazardous. Though operative deaths are now extremely rare, it is difficult to be enthusiastic about such a major operation on a baby. The outer membrane is often well formed and easily removed. It does, however, usually envelop both cerebral hemispheres, and therefore cannot be safely reached even through a large craniotomy opening. The inner membrane is sometimes so thin as to be almost unidentifiable, and again its removal must be far from complete. There are often bridging veins between the outer and inner membranes so that dissection at a distance from the craniotomy opening is sometimes hazardous. Fortunately this method of treatment apparently in many cases allowed expansion of the brain and the disappearance of subdural fluid.

In other patients, especially where there has been a substantial increase in head size, the brain is never able to expand sufficiently to fill the available space and the subdural collection of fluid inevitably remains. This led Ransohoff (1957) to perform a shunt operation in order to carry the fluid elsewhere over a long period of time, during which the disproportion between brain and skull could be corrected. He also mentioned that a shunting operation was carried out because craniotomy had failed to lead to a satisfactory reduction in intracranial pressure. In my view, however, it is probable that such failure is not uncommon whether or not disproportion exists between brain and skull. For this reason in recent years all subdural effusions have been treated by a subdural pleural shunt operation.

When the initial flow of fluid is large or when absorption is slow there may be temporary respiratory embarrassment. The babies are certainly in a better postoperative condition than those treated by craniotomy and the period of time in hospital is very much reduced. It is probable that the tubes (which do not require a valve) function for only a few weeks while the brain expands. The inner and outer subdural membranes either fuse or disappear, and the subdural space is eventually obliterated.

The actual development of the subdural effusion is only one factor of several which will determine the long-term quality of survival. Possibly the formation of subdural membranes is important, though there is no convincing proof of this. It can be accepted that failure to deal with the subdural fluid is likely to impair cerebral maturation, but the ultimate prognosis is related more to the underlying cortical damage which may have been inflicted at the time of the original injury or the attack of meningitis as the case may be.

The incidence of seizures and of mental retardation after treatment is probably independent of the method of treatment used. Shulman and Ransohoff (1961) provided results of small groups of patients treated either by craniotomy or by subdural pleural shunt. They found no significant difference in the proportions of children who were retarded or who suffered from seizures. The follow-up of patients in the present larger series indicates that the treatment by subdural pleural shunt may be superior to craniotomy. Nevertheless, the follow-up period is shorter here, so that assessment of impaired intelligence is more difficult and less accurate. There is no indication that treatment by craniotomy is in any way superior, and it is concluded, therefore, that this more elaborate procedure should be abandoned in favour of the simpler and less traumatic operation of subdural pleural shunt.

REFERENCES

Ransohoff, J. (1957). *Pediatrics*, **20**, 561.
Sherwood, D. (1930). *Amer. J. Dis. Child.*, **39**, 980.
Shulman, K., and Ransohoff, J. (1961). *J. Neurosurg.*, **18**, 175.

Relation between Headaches from Oral Contraceptives and Development of Endometrial Arterioles

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Brit. med. J., 1968, 3, 402–405

Summary: The incidence of headaches during the first year on oral contraceptives correlates closely with the incidence of well-developed arterioles in endometrial biopsy specimens. This relationship appears to depend on the ratio between progestogenic and oestrogenic components of the pill as well as the particular steroids. Therefore endometrial biopsies are useful for assessing the vascular response to an oral contraceptive and also provide a short cut to clinical evaluation of new formulations.

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Introduction

For the past six years clinical and endometrial studies have been carried out as part of the Council for the Investigation of Fertility Control central trial to evaluate new oral contraceptives. After the first year it was clear that, while dysmenorrhoea and premenstrual tension improved, headaches became more troublesome with Anovlar therapy (Mears and Grant, 1962). Groups of thick-walled arterioles were found in endometrial biopsy specimens obtained from women with these headaches (Grant, 1964). This observation was confirmed by Mazhar *et al.* (1965). In the normal cycle spiral arterioles and venous sinusoids develop in the late secretory phase, as described by

Noyes *et al.* (1950), who commented on interesting and variable changes in some cases. Grant (1965) described a headache-susceptible or vascular-reactive group of women from the appearance of their untreated endometrium—those who developed headaches on oral contraceptives were more likely to have well-developed arterioles in the proliferative and early secretory phases of the normal cycle. Mears (1967) has pointed out that the clinical effect of the various progestogen/oestrogen compounds depends on their hormone strengths and balance, which have been assessed by Grant (1967), who described three groups of compounds according to their endometrial effects and break-through bleeding incidence.

Group 1. Strongly Progestogenic.—These have a short growth phase, subnuclear vacuoles from days 8 to 11, and a prolonged atrophic or post-secretory phase. They have a low break-through bleeding incidence (0–3% of cycles).

Group 2. Intermediate.—These have variable growth, secretory, and atrophic phases with maximum subnuclear vacuoles between days 8 and 20. The break-through bleeding incidence varies from 4 to 40% of cycles according to the length of the secretory phase.

Group 3. Strongly Oestrogenic (particularly the sequential regimens).—These produced more growth and secretion than normal over a longer period but no post-secretory phase. They also have a low break-through bleeding incidence of 0–5% of cycles.

All predominantly progestogenic oral contraceptives have a similar endometrial pattern. Throughout most of the cycle the glands are small and inactive and the endometrium becomes progressively more atrophic with prolonged therapy. This makes it difficult to obtain specimens from every woman. However, each formulation appears to have a specific effect on arteriolar development throughout the cycle, irrespective of cycle day, which may be different from other compounds with a similar hormone balance, break-through bleeding incidence, and endometrial pattern. The biopsy specimens were obtained during routine examination at alternate visits, and no attempt was made to take them at any particular point in the cycle; it was found that the specimens obtained during treatment with each compound were evenly distributed throughout the cycle.

This paper describes the effect of various doses and combinations of progestogen/oestrogen formulations on the incidence of headaches, and how this appears to relate to the incidence of well-developed arterioles in endometrial biopsies.

Subjects and Methods

The organization and clinic routine of a Council for the Investigation of Fertility Countrol clinical trial and the characteristics of the healthy fertile volunteers have already been described in detail (Mears, 1961; Mears and Grant, 1962). At the central clinic a small number of patients, on many trial formulations, are under close observation. This includes endometrial biopsy examinations before the trial and at six-monthly intervals. At the same time detailed histories are taken of headaches, premenstrual tension, and other cyclic complaints. Table I lists the products included in this paper, the number of women enrolled on each, the duration of each trial, and the cycles completed. The endometrial biopsy specimens, which were obtained from days 5 to 30, were fixed in formalin, sectioned, and stained with haematoxylin and eosin. The slides were numbered and were examined without reference to clinical details. The tissue was measured, and the glands, stroma, and blood vessels were described. Arteriole groups were classified as inconspicuous when absent or small; or well-developed, which includes moderate groups and small arteries. To assess the untreated endometrial vasculature 284 pretrial biopsy specimens, obtained at the first visit of these women, were examined and grouped according to phase of cycle.

TABLE I.—*Effect of Various Oral Contraceptive Formulations on Headache Incidence*

Products (mg.)	Women	Cycles	Years of Trial	First-year Headache Incidence (% Women)
Ethynodiol diacetate 2 + mestranol 0·1 (Metrulen)	25	525	3	8
Ethynodiol diacetate 1 + mestranol 0·1 (Ovulen)	30	629	3	13
Ethynodiol diacetate 0·5 + mestranol 0·1	19	202	3	26
Ethynodiol diacetate 0·25 + mestranol 0·1	25	287	2	16
Ethynodiol diacetate 0·1 + mestranol 0·1	11	140	2	9
Norethisterone 2 + mestranol 0·1 (Ortho-Novin)	55	965	4	11
Lynoestrenol 2·5 + mestranol 0·075 (Lyndiol 2·5)	34	575	2	32
Norgestrol 3 + E.O. 0·05	9	96	1	33
Norgestrol 2 + E.O. 0·05	12	117	1	25
Norgestrol 1 + E.O. 0·05	28	430	3	50
Norgestrol 0·5 + E.O. 0·5	29	349	1	20
Norgestrol 0·25 + E.O. 0·05	31	183	2	19
Norgestrol 0·1 + E.O. 0·05	20	145	1	10
Norethisterone acetate 4 + E.O. 0·05 (Anovlar)	136	1,925	6	40
Norethisterone acetate 1 + E.O. 0·075	30	194	1	43
Norethisterone acetate 1 + E.O. 0·09	27	225	1	60

E.O. = Ethinyloestradiol.
Trade names of products subsequently marketed are shown in parentheses.

Results

Effect of Oral Contraceptives on Headaches

Most women found oral contraceptives so efficient and beneficial that few discontinued the method unless they had multiple complaints. In order of frequency these complaints were headaches, mood changes, vein changes, irregular cycles, and weight gain. The number of women stopping because of side-effects in the first year varied from 10 to 55% with different products. The overall follow-up rate was 95%. As women with complaints are more likely to withdraw in the early cycles, the incidence of side-effects appears to decrease in later cycles. For this reason we have quoted the number of women who noticed new or more persistent headaches on each product during the first 12 cycles, and not the headache incidence in successive cycles. The number of women affected varied from 8 to 60% (Table I), and appears to depend on the amounts of progestogen and oestrogen in the pill as well as the particular steroid components.

The typical "pill" headaches have already been described (Grant, 1965), and are often noted with the first few tablets. They usually occur in the intervals between courses of tablets, but may become continuous in a few cases. They are sometimes accompanied by nausea and vomiting. Some women experience dizziness, vertigo, flushing, or classical migraine preceded by visual disturbances. Meningism, transient cerebrovascular episodes, palpitations, chest pain, and hypertension have been known to develop in some cases after several years of therapy. These side-effects usually improve when the tablets are withdrawn, but the headaches may be exacerbated in a few cases.

The total headache incidence in 500 of these women before they joined the trial was 17%, including 7% who had migraine and 10% with premenstrual headaches (Grant, 1965).

Arteriolar Development in Normal Cycle

To assess the untreated endometrial vasculature 284 pretrial random biopsy specimens were examined and grouped according to phase of the cycle. Prominent arteriole groups were found in 6% of the specimens in the proliferative phase, in 11% in the early secretory phase, while there were 23% in the mid-secretory phase and 40% in the late secretory phase. Thus the proportion of samples containing conspicuous arterioles increased during the cycle. Most biopsy specimens taken in the late secretory phase have superficial arterioles but not always with well-developed walls. Sixteen per cent. of all the specimens had prominent arterioles.

Dosage and Arteriolar Development

The ethynodiol diacetate and norgestrol preparations show the effect of various doses of progestogen combined with a constant dose of oestrogen on arteriolar development. In 214 biopsy specimens obtained from 185 women taking ethynodiol diacetate preparations the variations in the proportions of well-developed arterioles at three dose levels (more than 0.5 mg., 0.5 mg., and less than 0.5 mg.) were significant ($\chi^2=12.7$; $P<0.01$) (Table II). Similarly, 105 specimens from 97 women taking the norgestrol preparations were also found to show significant variations in arterioles at three dose levels (more than 1 mg., 1 mg., and less than 1 mg.) ($\chi^2=14.2$; $P<0.01$) (Table III). As the dose of the progestogen was reduced the incidence of arteriolar development rose to a maximum and then decreased. In each case the dose which produced the maximum arteriolar development (0.5 mg. and 1 mg. respectively) was found to coincide with the dose having the highest headache incidence in the first 12 cycles (Table I). The critical dose level does not relate directly to the incidence of break-through bleeding, and therefore to hormone balance—for example, the 1-mg. norgestrol dose (subnuclear vacuoles days 7 to 11 and break-through bleeding 2%) is more progestogenic than the 0.5-mg. dose of ethynodiol diacetate (subnuclear vacuoles days 8 to 15 and break-through bleeding 15%).

TABLE II.—*Effect of Different Doses of Ethynodiol Diacetate + Mestranol 0.1 mg. on Endometrial Arterioles*

Ethynodiol Diacetate (mg.)	No.	Endometrial Biopsies. With Well-developed Arterioles		% B.T.B. Cycles
		No.	%	
2	26	3	12	2
1	69	6	9	4
0·5	62	19	35	15
0·25	26	4	19	40
0·1	31	2	6	25

B.T.B. = Break-through bleeding.
These results include 114 biopsy specimens from Dr. F. J. Morley.

TABLE III.—*Effect of Different Doses of Norgestrol + Ethinyloestradiol 0.05 mg. on Endometrial Arterioles*

Norgestrol (mg.)	No.	Endometrial Biopsies. With Prominent Arterioles		% B.T.B. Cycles
		No.	%	
3	12	2	16	0
2	11	2	18	1
1	36	18	50	2
0·5	11	2	18	3
0·25	22	1	5	10
0·1	13	1	8	40

Arteriolar Development and Headache

It was with Anovlar that arteriole groups were first noticed to be conspicuous in biopsy specimens from women with "subjective" complaints, especially headaches, and various other doses of norethisterone acetate and ethinyloestradiol were studied and found to produce similar effects (Table IV). Out of 20 women having biopsy examinations during treatment with norethisterone acetate 1 mg. and ethinyloestradiol 0.09 mg. 12 (60%) had well-developed arterioles, while 11 of these 12 had headaches in the first cycle. There was also a rapid weight gain with this product. Half the women gained an average of 10 lb. (4.5 kg.) in the first year. The same dose of norethisterone acetate with 0.025 mg. less oestrogen produced headaches in only 43% of the women.

Table IV shows the products in which the headache incidence and arteriole development could be compared in the same women. The headache incidence among these women over the same period ranged from 11 to 60% and correlates closely with the incidence of specimens showing arteriolar development. While a few of the women complaining of headaches had no obvious arteriole groups in their biopsy specimens, 84% (47 out of 56) had both at some time during the first year. The women showing most vascular reactivity also seemed to be most susceptible to other side-effects, such as mood changes and weight gain. It is of interest that the first-year drop-out rate was 10% with norethisterone 2 mg. + mestranol 0.1 mg. (Ortho-Novin) and 55% with norethisterone acetate 1 mg. + ethinyloestradiol 0.09 mg.

TABLE IV.—*Headache Incidence and Arteriolar Development in Women Who Had One or More Biopsy Specimens During Their First Year*

Product (mg.)	No. of Women	Headaches		Well-developed Arterioles		Both
		No.	%	No.	%	
Norethisterone 2 + mestranol 0·1 (Ortho-Novin)	18	2	11	2	11	1
Lynoestrenol 2·5 + mestranol 0·075 (Lyndiol 2·5)	25	8	32	9	36	8
Norgestrol 1 + E.O. 0·05	20	10	50	10	50	8
Norethisterone acetate 4 + E.O. 0·05 (Anovlar)	30	12	40	12	40	10
Norethisterone acetate 1 + E.O. 0·075	28	12	43	11	40	9
Norethisterone acetate 1 + E.O. 0·09	20	12	60	12	60	11
Total		56		56		47

E.O. = Ethinyloestradiol.

Discussion

Vascular reactions are the most frequent and troublesome side-effects of oral contraceptives. The commonest clinical manifestation of these is headache. Whereas the incidence of headaches in women before joining the trial was 17%, the incidence of headaches among the same women varied from 8 to 60% during treatment with different oral contraceptive formulations. The progestogen/oestrogen combinations which produce a high incidence of headaches also have a high incidence of endometrial arteriolar development. While this response depends to some extent on individual susceptibility, the most important factors are the exact dose and particular combination of oestrogen and progestogen. A change in dose of 0.015 mg. of ethinyloestradiol or 0.5 mg. of ethynodiol diacetate or norgestrol can significantly alter the headache incidence and arteriole development. This is not simply a question of total oestrogen or progestogen, as either alone does not have this effect to such a marked degree. Thus the arteriole effect seems to depend on a critical ratio of progestogen and oestrogen which can be established only by testing each combination of steroids at different doses.

The results suggest that changes in the endometrial vasculature may parallel changes in vessels in other parts of the body. To study this possibility retinal photographs were taken on the same day as endometrial biopsy specimens in 26 cases. However, the retinal vessels showed no obvious changes in the early cycle to compare with those in the endometrium. This may be because endometrial vessels are more sensitive and show hormone effects more quickly than vessels elsewhere. It is of interest that after five years on one oral contraceptive one of the women developed hypertension and had a cerebral thrombosis with secondary haemorrhage. The leptomeningeal vessels in the tissue obtained at operation showed thickening without obvious atheroma (J. M. Anderson, personal communication, 1967). While Walsh *et al.* (1965) have described a variety of neuro-opthalmological vascular changes in oral contraceptive users, Bickerstaff and Holmes (1967) and Illis *et al.* (1965) have suggested an association between the use of oral contraceptives and episodes of cerebral artery insufficiency.

Other important endometrial vascular effects of oral contraceptives are dilatation of sinusoids and stromal condensation round their walls. These appear to be related to vein changes

in the legs and elsewhere, as will be described in a separate paper.

I gratefully acknowledge the help which I have received from Dr. Eleanor Mears and the Council for the Investigation of Fertility Control, also the financial assistance from the Lalor Foundation. I also thank Dr. Hilary Hill, Dr. J. Pryse-Davies, Dr. F. J. Morley, Dr. B. Schooling, Dr. R. Tozer, Dr. T. King, Dr. J. Scott-Wilson, and Mrs. B. Lamb for contributing to this study. I am indebted to Mr. B. Mathalone and Dr. A. Bron, who carried out ophthalmological examinations and photography at Moorfields Eye Hospital, and to Mrs. Ann Davis for statistical analysis.

REFERENCES

Bickerstaff, E. R., and Holmes, J. MacD. (1967). *Brit. med. J.*, 1, 726.
Grant, E. C. G. (1964). *J. Reprod. Fertil.*, 8, 275.
Grant, E. C. G. (1965). *Lancet*, 1, 1143.
Grant, E. C. G. (1967) *J. Obstet. Gynaec. Brit. Cwlth*, 74, 908.
Illis, L., Kocen, R. S., McDonald, W. I., and Mondkar, V. P. (1965). *Brit. med. J.*, 2, 1164.
Mazhar, K., Hefnawi, F., Kadri, Sh., El-Ganzoury, B. A., Askalani, A. H., and El-Tagi, A. H. (1965). Paper presented at symposium on Family Planning, Cairo.
Mears, E. (1961). *Brit. med. J.*, 2, 1179.
Mears, E. (1967). In *Excerpta Medica International Congress Series* No. 133, p. 1005. Amsterdam.
Mears, E., and Grant, E. C. G. (1962). *Brit. med. J.*, 2, 75.
Noyes, R. W., Hertig, A. T., and Rock, J. (1950). *Fertil. Steril.*, 1, 3.
Walsh, F. B., Clark, D. B., Thompson, R. S., and Nicholson, D. H. (1965). *Arch. Ophthal.*, 74, 628.

Circadian Rhythm of Plasma 11-Hydroxycorticosteroids in Psychiatric Disorders

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Brit. med. J., 1968, 3, 405–407

Summary: Studies of the circadian rhythm in plasma 11-O.H.C.S. levels showed that a subgroup of affective psychotics had higher plasma 11-OHCS values as compared with schizophrenic and other psychotic subgroups, and a somewhat less regular rhythm. One patient with depression who was studied over 48-hour periods showed a reduction in plasma 11-OHCS levels with clinical recovery. An accentuated fall and rise in plasma 11-OHCS values in the night and early morning samples, respectively, was observed in the schizophrenic subgroup.

Introduction

Psychiatric disorders are sometimes associated with changes in physiological rhythms. Manic-depressive illness is an outstanding example, with daily variations in mood and symptoms and disruption of the normal pattern of sleep and wakefulness. Changes in the amplitude of water, potassium, sodium, and chloride excretory rhythms have recently been noted in this condition (Lobban *et al.*, 1963; Elithorn *et al.*, 1966). Abnormalities of urine volume and diurnal rhythm have been reported in schizophrenia (Gjessing, 1936; Hoskins, 1946; Randrup and Munkvad, 1966), and the onset of this disease is sometimes marked by a prolonged period of wakefulness (Bliss *et al.*, 1959).

Adrenocortical secretion in healthy subjects is known (Pincus, 1943; Bliss *et al.*, 1953) to have a 24-hour, or circadian, rhythm and has been shown to be very closely associated with the sleep-wakefulness cycle, peak plasma corticosteroid levels occurring shortly before awakening, and minimum values about midnight (Perkoff *et al.*, 1959). Disturbances of adrenocortical secretion in psychiatric illness have been suspected for some time, particularly in depressive illness (Reiss, 1953) and to a lesser extent in schizophrenia (Hoagland *et al.*, 1953).

We describe here observations on the circadian rhythm of plasma 11-OHCS in manic-depressive and schizophrenic patients and in patients suffering from psychiatric disorders not considered to be associated with disturbances of the sleep-wakefulness cycle. A pilot survey has already been reported (Conroy *et al.*, 1968).

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Patients and Methods

In one investigation 16 patients, all men, were divided into three subgroups, A, B, and C, consisting respectively of five schizophrenics, six affective psychotics, and five patients with psychotic illnesses not marked by disturbances of sleep. All the schizophrenics displayed first-rank Schneiderian symptoms. The six affective psychotics had a characteristic history of phasic alternation of mood together with early morning waking, significant self-reproach, constipation, bowel preoccupation, and anorexia in the depressive phases. Four of the six had a previous history of episodes of hypomania.

None of the schizophrenics complained of regular disturbance of sleep, while the depressed patients all complained of insomnia—in particular early morning wakefulness, which was present at the time of investigation.

All the schizophrenics were being treated with phenothiazines—mainly chlorpromazine and trifluoperazine—and the affective psychotics, who were all in the depressive phase, were receiving imipramine or amitriptyline.

The other psychotics comprised two patients with presenile dementia, two cerebral arteriosclerotics, and one patient with Korsakoff's syndrome.

The subjects were living under a similar regimen in a psychiatric hospital. With the exception of one schizophrenic all had been admitted at least three months before the investigation. Drug therapy was discontinued for the 24 hours preceding the first blood sample. The samples were obtained at 10.00, 14.00, 18.00, 22.00, 02.00, 06.00 hours, and again at 10.00 hours (± 1/4 hour in each instance).

Four patients, all female, two of them affective psychotics and two suffering from schizophrenia, were observed in a second investigation extending over a period of up to 12 months. The two affective psychotics had a long history extending over 10 years of periods of depression alternating with hypomania with normality in between. Both schizo-