a positive personal or family history of migraine, and had E.E.G.s which showed more abnormalities suggestive of latent migraine than those of controls on oral contraceptives who were headache-free. Moreover, these abnormalities persisted in those who had repeat E.E.G.s after discontinuing the pill, which suggests that the vascular abnormalities pre-existed.[1] In view of Dr. Grant's finding of prominent arterioles in 16% of pre-treaunent endometrial biopsies, it would seem reasonable to postulate a widespread vascular hyperreactivity, which frequently manifests as headache on oral contraceptives.

My findings do not show the same specificity of response to the particular oestrogen/progesterone combination as do Dr. Grant's. In my series, the incidence of severe headache on Anovlar (norethisterone acetate, ethinyloestradiol) was 3.2% (compared with Dr. Grant's 40%); 1.7% with Lyndiol (lynoestrenol, mestranol) (Dr. Grant 32%) and 6.2% with Ovulen (ethynodiol acetate, mestranol) (Dr. Grant 13%). Moreover, headaches frequently persisted despite changing to another brand with a different combination once (23%), twice (15%), three or more times (7%) in an effort to overcome the headaches.—I am, etc.,

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SIR,—There are a few comments which I would like to make about the paper by Dr. Ellen C. G. Grant on the relation between headache, oral contraceptives, and the incidence of well-developed endometrial arteries (17 August, p. 402).

One of the major difficulties of studies into the incidence of subjective symptoms is in the collection of adequate and carefully regulated control data. It is well known that patients do not retain an accurate memory for symptoms of the more common type over a long period, and that such data can prove exceedingly unreliable when related to side-effects of oral contraceptives.[1] However, in this paper the only control material available[2] relates to patient's history—retrospective—and is compared to a prospective analysis of greater depth, at least two interviews over the year of study, a procedure which can give rise to highly misleading results.[1] In addition, such methods of obtaining control data have the great disadvantage of alerting the patients to the possibility of headache on drug therapy. Adequate control material can only be obtained by running a group concurrently with the one undergoing medication, that is, perhaps, with an intrauterine device, etc., the interviewer remaining blind to the treatment the patient is receiving. It is not possible for the patient to be blind because of the nature of medication, that is either you are on the pill or you are not on the pill. A placebo group would be ruled out for obvious reasons. Only by this method can the spontaneous development of headache be taken into consideration and observer bias removed. Patient bias, unfortunately, would still remain.

The method of collecting data has given rise to another difficulty created by the method of expressing the results, namely the headache incidence, as a percentage of women receiving treatment in the first year. It is unlikely that pretreatment interview relates to a history of more than a few months' duration. If we take the spontaneous incidence of a woman complaining of headache from one interview as 17%, two interviews over the period of a year would give an overall frequency of at least 30% if expressed as above. This figure is the one to which comparison shall be made. As stated before, it is not possible to be exact about this percentage without an adequate control procedure being followed. However, it would mean that only four out of the 16 trial combinations would materially fall above this. In addition, this estimate is likely to be on the low side because of the lack of knowledge about a spontaneous development of headache in a population so fraught with emotional overtones as that requiring family planning. Would one, therefore, be justified in stating that Ovulen (ethynodiol acetate), Ortho-Novin (norethisterone, mestranol), Lyndiol 2.5 (lynoestrenol, mestranol), and Ovran (norgestrel) caused a considerable decrease in headache incidence compared with that present in the non-treated female population, as is suggested by some investigators ?[1]

In addition it is unclear whether the diagnostic groupings of headache in the pre-treatment assessment, namely migraine and premenstrual headache, both of which are fairly well defined clinically, can be compared with those obtained on treatment, where it would appear that "headaches" generally were included. Were only "typical pill headaches" included or were other types such as psychologically induced tension headaches excluded? Headache as a clinical term contains so many different conditions of different aetiologies, ranging from migraine to meningitis or mercurial poisoning, that some differentiation into the type of headache should be endeavoured. In essence, therefore, no valid conclusion can be drawn from material of this type without adequate control data being available, and some attempt at categorizing the all-embracing term of headache into something which is more clinically meaningful.—I am, etc.,

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E.C.G. and Tricyclic Antidepressive Drugs

SIR,—It is known that the tricyclic antidepressive drugs imipramine[1 2] and amitriptyline[3] may produce arrhythmias and E.C.G. changes in cases of poisoning, and with imipramine these changes have also been reported during therapeutic use.[4] The effects produced comprise various A–V arrhythmias, widening of the QRS complex, and displacement of the S–T segment. Recently Drs. R. J. Barnes, S. M. Kong, and R. W. Y. Wu (27 July, p. 222) have suggested a diagnostic application of these findings to distinguish poisoning by the tricyclic antidepressive agents from other types of drug poisoning. However, there are both animal and clinical data which suggest that this diagnostic aid may not be generally applicable, because the cardiac action of the related, but indole-based, tricyclic drug iprindole[5] appears to differ from that of imipramine and amitriptyline.

In anaesthetized animals a comparison has been made of the effects of iprindole, imipramine, and amitriptyline administered intravenously in cumulative doses of 1 to 5 mg./kg. in rats and 1 to 25 mg./kg. in cats. In both species all three compounds reduced the blood pressure and caused temporary apnoea, and, particularly in the rat, there was also transient bradycardia with A–V block and occasional premature atrial systoles lasting less than two minutes. The bradycardia and arrhythmias were most pronounced with iprindole, but imipramine and amitriptyline were more respiratory depressant and were lethal to both rats and cats in lower doses. Apart from its transient effect on cardiac rhythm, iprindole had little or no effect on the configuration of the electrocardiogram, whereas both imipramine and amitriptyline had an additional and almost immediate effect in increasing the S wave voltage of lead II, with widening of the Q–T interval and displacement of the S–T segment lasting up to one hour in the cat. These findings suggest that although iprindole shares with imipramine and amitriptyline the ability to produce transient changes in cardiac rhythm, perhaps associated with an effect on the autonomic innervation of the heart, it does not share their ability to produce those changes in the cardiac muscle responsible for alterations in the electrical complex itself.

In therapeutic use iprindole has approximately the same antidepressive potency as imipramine, but it produces fewer anticholinergic side-effects and has not been observed to cause electrocardiographic changes. Imlah[6] has described the effects of iprindole in two groups of four patients treated continuously with daily doses of 45 and 90 mg. for more than 12 months, but no changes were found in the E.C.G.; similarly, no electrocardiographic changes were found in six patients treated with daily doses of 90 mg. iprindole for six weeks.[7] Although no case of poisoning with iprindole alone has yet been reported, the evidence indicates that the drug is unlikely to produce those changes in the electrocardiographic configuration which Dr. Barnes and his colleagues described as diagnostic for poisoning with other tricyclic antidepressive agents.—We are, etc.,

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Purpura and Paracetamol

SIR,—In view of the rarity of untoward side-effects from therapeutic doses of paracetamol, the following case report may be of interest.

A 63-year-old woman had been receiving adequate therapy of cyanocobalamin and thyroxine for some years following a well-substantiated diagnosis of pernicious anaemia and hypothyroidism. In addition, for five