neuromusculature is a highly probable sequel to persistent purging.

Dr. Smith's suggestion that the sennosides have an affinity for the colonic myenteric neurones finds some support from the work of Okada,[3] and Straub and Triendl,[4] and if confirmed would show the sennosides to be extremely selective in their therapeutic action. However, Dr. Smith's suggestion is, we feel, likely to prove an over-simplification of the position, which must take into account such aspects as the release of the active fraction of the sennosides by interaction with colonic microflora within the gut lumen.[3 5]

In the meantime, as is the case with many drugs, clinical experience of the therapeutic effects of the sennosides has far outstripped the knowledge of their pharmacology, and the immediate clinical significance of the investigation of Dr. Avery Jones and Dr. Barbara Smith is to emphasize in a new and important way the great harm which can result from the misuse of laxative drugs. Unfortunately the problem of laxative abuse by the lay public remains.—I am, etc.,

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Headache on the Pill

SIR,—Dr. Ellen C. G. Grant (17 August, p. 402) reports that the incidence of headache on six oral contraceptive formulations varied between 11–60% (Table IV), a variation of nearly sixfold. It is well recognized that variation in the reported incidence of headache and other symptoms is dependent not only upon the formulation under evaluation but also upon the centre or the individual doctor within the centre. For example, Hines, Goldzieher, and King[1] have reported a variation between centres in reported first cycle headache of approximately fourteenfold and an even greater variation in first cycle nausea in a large-scale multicentre study in which only *one* formulation was under evaluation. To quote these authors "... the variation from center to center is beyond that of random sampling ..." and again "... the variation among centers must be due to some combination of different patient populations and different questioning technics at the different centers."

We are at present involved in a multicentre evaluation of several different oral contraceptives. It has become quite clear from the preliminary analysis of the data that variations between different observers in the reported incidence of several symptoms, including headache, considerably outweigh the variation which can be attributed to differences in formulation or differences between the patients seen at the several centres. In view of these findings I am led to wonder whether all the patients were always seen by a single doctor at the Council for the Investigation of Fertility Control trial centre, and if not whether due allowance has been made for between-doctor variations in reporting rate. I feel that Dr. Grant's answers to this question are vital to a proper evaluation of the data she has presented in her paper.—I am, etc.,

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REFERENCE

1 Hines, D. C., Goldzieher, J. W., King, E. P. In *Proceedings 5th World Congress of Fertility and Sterility*, Excerpta Medica International Congress Series, No. 133, 1967, p. 1038, Amsterdam.

SIR,—May we comment on some of the points raised in your leading article (17 August, p. 388) which related to the article by one of us (17 August, p. 402)?

Although this paper dealt only with the 19 nor-progestogens, we have found headaches and well-developed endometrial arterioles to occur with all the synthetic progestogens and oestrogens we have tested, including the hydroxy progestogens, megestrol acetate and chlormadinone. While these headaches on combined therapy usually occur in the interval between courses and are therefore likely to be due to vascular changes from withdrawal of hormones, this is not always so, especially in the more severe cases, when they are sometimes associated with the medication. We have also found severe headaches in some women while on oestrogen alone, as in the first part of a sequential regimen. You state that there does not appear to be any association between oestrogens dispensed on their own for other indications and headaches. It seems, however, that the side-effects of oestrogen therapy were not adequately studied until recently despite widespread use over some 30 years. For example, it is only now that an association is suggested between giving stilboestrol to inhibit lactation and an increase of thromboembolism, and oestrogens were freely available over the counter without prescription until April 1960. We have found a significantly higher incidence of vein complaints and of thromboembolic phenomena among women on combined oral contraceptive tablets which are weakly progestogenic (breakthrough bleedings 4–40%) and contain mestranol than with the other types (paper in preparation).

Recently we have examined 108 endometrial biopsies taken from women on low-dose continuous progestogen taking part in a trial in which four different progestogens are being used, namely, norethisterone acetate 0.3 mg., norgestrol 0.05 mg., chlormadinone 0.5 mg., and megestrol acetate 0.25 mg. The only one which gave a normal endometrium and virtually no side-effects (megestrol acetate) also gave 17 pregnancies in the 44 women taking it. It appears that the dose of progestogen used was too low to suppress endogenous oestrogen and this has since had to be increased. With the other three progestogens the dose has been adequate to control fertility (pregnancy rate between 2 and 8%) and the appearance of the endometrium was very similar to that of the weakly progestogenic combined oral contraceptive formulations. Only 18% of the chlormadinone 0.5 mg. specimens were compatible with a normal ovulatory cycle One of the progestogens (norgestrol 0.05 mg.) produced arteriolar development in 28% of the endometria studied. From these endometrial findings we would expect the same type of side-effects from low-dose continuous progestogen as with the weakly progestogenic combined pills, with possibly a lower incidence in the first year.

As you say, the case of low-dose progestogens is by no means established, and indeed it seems premature to expect too much of them until they have been properly investigated. Important though it is to continue the search for simpler and safer contraceptive methods we must not wait for them to deal with problems which exist now. Present oral contraceptives and intrauterine contraceptive devices have been the most important factors where success has been achieved in population problems in recent years, and we must make sure that they are taken full advantage of until other methods do become available. —We are, etc.,

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Propranolol in Myocardial Infarction

SIR,—We have read with great interest the article by Dr. R. M. Norris and colleagues (18 May, p. 398) on the use of propranolol to reduce the mortality in acute myocardial infarction. We should like to comment on their—in some respects—negative results.

Their patients were not grouped according to whether they were one, two, or three days post infarction. This information is vital, for the simple reason that the tendency for fatal arrhythmias decreases as each day passes. Thus evaluation of sudden death in the treated group does not give a true picture. Furthermore, the inconstancy of blood levels of propranolol given orally makes this method of administration unsatisfactory at the time of greatest risk, and conclusions drawn from this method of treatment cannot be accepted as convincing.

In our own department propranolol was given by slow-drip infusion to 50 patients with acute myocardial infarction who had been admitted to hospital within 24 hours, but who did not have signs of extensive myocardial damage, or cardiac failure, or appear clinically to be shocked. Two of these patients died of ventricular fibrillation. In a group of 44 patients not treated in this fashion there were nine fatal cases. Thus, in our own experience, propranolol administered by slow-drip infusion suppressed cardiac arrhythmias and reduced mortality.—I am, etc.,

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SIR,—Dr. D. A. L. Watt (17 August, p. 413) draws attention to fatal results arising from the treatment of digitalis overdosage by propranolol. Considering the large number of elderly patients on digoxin and frequently having an overdose Dr. Watt's article is surely sufficient warning against using propranolol. Yet in *Prescribers' Journal*[1] I read: "Propranolol ('Inderal') ... One major indication for it is the treatment of tachycardia caused by digitalis poisoning."