METHOD

Full clinical histories, including details of premenstrual tension and previous mental illnesses, were obtained from volunteers attending the central clinic of the Council for the Investigation of Fertility Control. A total of 797 women received one or more of 34 oral contraceptives (Tables I and II), giving a treatment experience of 1,217 women. The incidence of depression, loss of libido, tiredness, and irritability occurring with the various formulations was observed over six years.

Endometrial biopsies were obtained, at all stages of the cycle, before treatment and thereafter during routine six-monthly examinations. The 137 biopsies studied were obtained at random from women taking the products being tested during a one-year period. The various products have been grouped according to endometrial effect and break-through bleeding incidence (Grant, 1967) as strongly progestogenic, strongly oestrogenic, and intermediate compounds. They have been further subdivided according to oestrogen content (Table III). The specimens were examined without previous knowledge of clinical details. Curetted fragments were frozen immediately after removal, and sections were prepared and examined as described by Southgate *et al.* (1967). Monoamine oxidase activity was demonstrated by the method of Glenner *et al.* (1957). Alkaline and acid phosphatase were demonstrated by an azo dye coupling method, Fast Red LTR (Pryse-Davies *et al.*, 1961).

CLINICAL RESULTS

Tables I and II show the percentage of women complaining of depression and loss of libido on the individual preparations. These are grouped according to hormone balance and type of oestrogen in Table IV. The incidence of depression and loss of libido ranged from 28% of women on strongly progestogenic preparations containing ethinyloestradiol to 7% of women on the strongly oestrogenic sequential regimens containing ethinyloestradiol and 5% on the sequentials containing mestranol: these figures differ significantly ($P<0.01$) from the average incidence of 16% for all women in Table IV. Thus the incidence of depression and loss of libido are greatest with the strongly progestogenic oral contraceptives containing a small dose of oestrogen. Two of the 136 women taking Anovlar (norethisterone acetate 4 mg.+ethinyloestradiol 0.05 mg.) became sufficiently depressed to attempt suicide. Though Lyndiol (lynoestrenol 5 mg.+mestranol 0.15 mg.) is strongly progestogenic (break-through bleeding 2%) it also contains a high dose of mestranol and has a low incidence of depression and loss of libido, whereas Volidan (megestrol acetate 4 mg.+ethinyloestradiol 0.05 mg.) is less progestogenic (break-through bleeding 10%) but contains a low dose of ethinyloestradiol and has a high incidence of depressive change.

Other mood changes noted were tiredness, irritability, aggression, and increased libido. These could not be related to hormone balance but may be influenced by vascular changes. Aggression was particularly noticeable with norethisterone acetate 1 mg. and ethinyloestradiol 0.075 mg., which had a marked effect on the development of both arterioles and sinusoids in the endometrium. Premenstrual tension, which was a common complaint before the trial, especially in older women, almost invariably improved. Only a few women discontinued the tablets because of mood changes in the early cycles, but over the period of the trial 40% of those withdrawing for side-effects had at least one mood complaint.

HISTOCHEMICAL RESULTS

Fig. 1 shows the activities of the three enzymes according to the day of the cycle. In the untreated groups (I and VI) the late secretory phase is also indicated.