volunteers received glutethimide 500 mg every evening for five days. Twenty-four-hour D-glucaric acid excretion was measured on a control day and daily thereafter. The results are shown in the figure.

D-glucaric acid excretion (mean ± SEM) in three healthy male subjects given glutethimide on days 2 to 6.
Conversion: SI to traditional units—D-glucaric acid: 1 μmol/l ≈ 132 μg.

There was clear evidence of enzyme induction within two days of the first administration. As change in D-glucaric acid excretion has been shown to correlate with change in antipyrine half life⁴ important drug interactions could be expected at this time. Changes in steady-state plasma levels of warfarin would take much longer to develop because of the drug's long half life. These results suggest, however, that as little as two doses of glutethimide could alter the dosage requirements of drugs with shorter half lives such as cortisone.

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Progesterone or progestogens?

SIR,—Your expert's answer (11 September, p 634) to the question "Does progesterone have a place on treating premenstrual and postpartum depression?" assumes, quite falsely, that progestogens are a convenient oral substitute for the natural hormone progesterone. They are not, and medical advances in psychiatry, gynaecology, and obstetrics are held up by the failure of clinicians to appreciate this fact. Both are valuable drugs with specific indications for their use.

By definition progestogens are drugs which cause endometrial withdrawal bleeding in immature oestrogen-primed rabbits (Clauberg's test) in the same manner as progesterone. On this test many progestogens are more potent than progesterone; D-norgestrel is 2000 times more potent. However, whereas progesterone causes endometrial hypertrophy, some progestogens cause endometrial atrophy. Some are oestrogenic—for example, 19-

nortestosterone derivatives—and other progestogens are free from oestrogenic activity—for example, medroxyprogesterone. Some, especially the 19-nortestosterone derivatives, are androgenic and in pregnancy cause masculinisation of the female fetus, but progesterone is completely free from androgenic effects on the fetus.¹ Progestogens, in fact, cause a reduction in plasma progesterone whereas, of course, progesterone does not.²

Progesterone is also formed in the adrenals, where it is converted from cholesterol and becomes the precursor of all corticosteroids. Progesterone is responsible for the transport of glucocorticoids attached to the alpha globulin of the plasma and it is one of the few steroids with a high affinity for this binding protein and can cause displacement of cortisol to the free active fraction.³ These glucocorticoids maintain liver glycogen and help to maintain the blood sugar levels. Progestogens cannot mimic these actions of progesterone.

Progestogens are the drugs of choice as contraceptives and where endometrial atrophy is required, as in endometriosis and menorrhagia. Progesterone is the drug of choice in premenstrual and postpartum depression and premenstrual syndrome. Progesterone cannot be absorbed orally but has good absorption by the vaginal and rectal routes.⁴ As the biological half life of progesterone is short the dose and timing of administration is crucial if physiological levels are to be maintained and this may call for twice-daily administration.

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* * * Our expert writes: "I am aware of Dr Dalton's work but I have found that people do get better on the treatment I advocated—Ed, BMJ.

Low-dose progestogens and ectopic pregnancy

SIR,—The low-dose progestogens account for about 35% of all oral contraceptives now used in Finland. In this department we have found a total of 15 cases of ectopic pregnancy in patients using low-dose progestogens for contraception in the period from 1 January 1973 to the end of August 1976. Table I shows the total number of ectopic pregnancies and the number and incidence of ectopic pregnancies during low-dose progestogen contraception annually in this period. Table II

TABLE I—Total number of ectopic pregnancies and number and incidence of ectopic pregnancies during low-dose progestogen contraception

Year	Ectopic pregnancies	Ectopics during progestogen contraception	%
1973	37	1	2.7
1974	52	4	7.7
1975	47	7	14.9
1976 until end of August)	37	3	8.1
Total	173	15	8.7

TABLE II—Calculated use of different progestogens in women years, number of ectopic pregnancies in 1973-5, and risk of ectopic pregnancy for each progestogen

Progestogen	Use in women years	Ectopic pregnancies	Risk of ectopic pregnancy per year (%)
D-Norgestrel 0.03 mg ..	1600	7	0.44
Norethisterone 0.3 mg ..	1000	4	0.40
Lynoeestrol 0.5 mg ..	4200	1	0.02

shows cases of ectopic pregnancy for different progestogens used for contraception.

On the basis of these figures it is possible to estimate the absolute risk of ectopic pregnancy carried by different progestogens (table II). Thus for D-norgestrel 0.03 mg the risk is approximately 1 per 230 users and for norethisterone 0.3 mg 1 per 250 users per year. Lynoeestrol 0.5 mg has a very significantly ($P < 0.001$) smaller risk of 1 per 4200 users per year. According to the manufacturers the Pearl index for D-norgestrel is 1.0, for norethisterone 1.4, and for lynoeestrol 0.4. If the figures are true it can be estimated that almost every second pregnancy with D-norgestrel and every third with norethisterone are ectopic. For lynoeestrol this risk is one ectopic pregnancy in 17 pregnancies.

Our study confirms the suggestion^{1,2} that the risk of ectopic pregnancy is considerable among the users of low-dose progestogens. Our study also shows that certain preparations carry an exceptionally high risk of extrauterine pregnancy. From a therapeutic point of view, the possibility of ectopic pregnancy has to be considered whenever the low-dose progestogens are prescribed for contraceptive purposes. Also the possibility of ectopic pregnancy must always be taken into consideration in patients developing pain in the lower abdomen while on low-dose progestogens, irrespective of their previous bleeding pattern.

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Prazosin in hypertension

SIR,—I note with interest Professor Clive Rosendorff's observations (28 August, p 508) concerning the dose dependency of the initial side effects of prazosin. In this department we have used this hypotensive agent on over 150 patients and confirm his findings.

Recently 24 hypertensive patients (12 female) were studied with a single 1-mg tablet. Supine and erect blood pressures were recorded at 15-min intervals before and after the dose for up to 270 min. Six had had no previous therapy and 18 were uncontrolled on other drugs, chiefly thiazides or beta-blockers or a combination of both. In 10 there were no symptoms of postural hypotension. In this group there was a mean maximum erect blood pressure reduction of 22/14 mm Hg (from 165/109 mm Hg) at an average of 110 min after the dose. The mean pulse rate remained unchanged. The remaining 14 patients had symptoms of postural hypotension; in three