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

these were mild, in eight moderate, and in three severe. Two patients with severe symptoms were pale and sweating, with almost unrecordable diastolic pressures, and the clinical picture suggested peripheral blood pooling with low cardiac output. The mean maximum erect pressure reduction was 63/48 mm Hg (from 165/112 mm Hg) at a mean of 90 min after the dose. Mean pulse rate rose 10/min. Postural hypotension lasted up to four hours in 11 patients and up to seven hours in three. Two severe reactors had had no previous drug therapy. Subsequently 22 additional patients were studied in the same manner with a single dose of 0.5 mg, 11 of them in a double-blind within-patient crossover study with placebo. There were no significant postural symptoms in this group and there was a mean maximum fall in erect diastolic pressure of approximately 25 mm Hg.

These observations indeed confirm that initial symptoms of postural hypotension after the first dose of prazosin are dose-dependent and that the initial dose should not exceed one 0.5-mg tablet. Many of these patients were subsequently treated with prazosin. Doses of thiazides and beta-blocking agents were not increased and in some cases were reduced. Our preliminary observations suggest that the therapeutic response may be better and the dose of prazosin required may be lower in those patients in whom the hypotensive response to the first dose is abrupt. We believe that a significant initial postural fall in blood pressure may be indicative of a subsequent satisfactory response to this very useful drug.

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Possible association of Madelung's deformity with Huntington's chorea

SIR,—Recently correspondents have discussed in your columns (3 July, p 46; 14 August, p 420) the desirability of publicity directed at the lay public concerning Huntington's chorea. As a direct result of this publicity a member of a Huntington's chorea family has approached me for assistance in clarifying their family history. A diagnosis of Parkinson's disease had been made in a member of the family who would have had to have Huntington's chorea to substantiate the subsequent diagnoses. On studying this family it became apparent that a wrist deformity (possibly Madelung's deformity) was also inherited as a dominant condition. It also appeared that the wrist deformity was inherited only by those members who went on to develop Huntington's chorea.

Although the members of this family have not been seen in person, considerable correspondence has taken place with them and their medical practitioners and it was felt that the family needed to be investigated more thoroughly as there was a possibility of a linkage between the wrist deformity and Huntington's chorea. To this end a request was inserted in the latest newsletter of the Association to Combat Huntington's chorea for news of any people in choreic families who also had a wrist deformity. To date there has been one reply from a young woman in such a family who states that she has Madelung's deformity which was successfully operated upon some years ago. Although Madelung's

deformity is very unlikely as a genetic link in all cases of Huntington's chorea, there appears to be a strong possibility of it being linked in the family originally investigated. The next step must therefore be to trace the family of the young woman with Madelung's deformity to see if she is related to the original family, and a continuing search must be made for other patients in whom these dominant diseases coexist. Madelung's deformity sometimes shows up only radiographically, so it is hoped that x-ray films of the wrists of all members of these families will be undertaken.

In the meantime we must again look at the question of ethics with regard to counselling such a family. Should this link prove to be predictive, could it in all fairness be used when we have nothing in terms of treatment to offer the unfortunate carriers of the gene? This was the problem the levodopa provocation test produced some years ago, as discussed in the *BMJ*.¹ The majority solved this problem by not using levodopa. An obvious wrist deformity is much less easy to ignore.

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¹ *British Medical Journal*, 1972, 3, 540.

Immunofluorescent sperm antibodies in virgins

SIR,—Your recent leading article on antibodies to spermatozoa (2 October, p 774) appeared to recommend the use of immunofluorescent techniques and staining patterns to distinguish between normal and pathological autoantibodies.

From previous studies on infertile patients¹⁻³ I cannot share this enthusiasm, as a large number of positives were not only found in infertile couples but also in control groups with no particular pattern or titre appearing significant. There are, however, potential errors in the use of serum from pregnant or previously pregnant patients as control. To allay any such criticisms serum from virgins was tested for sperm antibodies by the indirect immunofluorescent technique on the rationale that females who have never had contact with spermatozoa should not have circulating sperm antibodies.

Serum from 66 informed virgin volunteers aged between 18 and 45, obtained from random sources, was tested for the presence of antibodies against sperm at a titre of 1 in 25 by the indirect immunofluorescent technique, with and without methanol fixation.¹ From table I it can be seen that positives were

TABLE I—Immunofluorescent sperm antibodies: virgin serum

Total No	No positive
66	20 (30%)

TABLE II—Positive immunofluorescence patterns: virgin serum

Equatorial	Tail	Postnuclear cap	Mid-piece	Achrosomal	More than one pattern
21%	29%	8%	0	41.6%	20%

obtained from 20 (30%) of these virgins, which surely is indictment enough of any method. From table II it would also appear that examination of the staining pattern is of little help, for all patterns were found to be present, except mid-piece, with achrosomal the most common. Indeed, more than one pattern was present in 20%.

This high number of positives in a group of subjects who should be negative reflects the intrinsic weakness of the method. False-positives may occur due to cross-reaction with bacterial antibodies,⁴ non-specific binding of immunoglobulins,⁵ or involvement of antibodies from beneath the cell membrane of the sperm.⁶

It would therefore appear that the indirect immunofluorescent test is of little value as a measure of sperm antibody presence, and, although it may be a more acceptable immunological test than some of the others available, the question of the significance of sperm antibodies as a cause of infertility cannot be answered by its use.

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Teaching of anatomy

SIR,—Having read with keen interest your leading article on this subject (11 September, p 603), I wonder whether I could give my views as an anatomist teaching in Germany.

I have just returned from a most stimulating meeting on "computerised axial tomography" in London (11-15 October). This meeting and the enormous progress made by British inventiveness offer a very stimulating challenge to the anatomist who teaches clinical or topographical anatomy. Axial tomography has enlarged the scope of anatomy teaching enormously, a subject which can only be taught in its clinical implications by medically trained lecturers. Clinical students, clinicians, and radiologists have now to know more anatomy, not less, and have to adapt their teaching to the new demands of axial tomography, demanding more anatomy from a clinical diagnostic point of view. But your leading article clearly points out that anatomy is taught on a very much reduced scale in Britain. In Germany standards have been very significantly and drastically cut—for example, dissection of the body has been reduced to one winter term only. Altogether the preclinical curriculum has been reduced from five terms to four—two summer terms and two winter terms. Two terms account for about 5½ months of one year. While term work has thus been reduced, new subjects