Once an adrenal origin has been excluded the treatments available for PCO are temporary or symptomatic. Clomiphene can only be used short term under well-controlled conditions in women who want to have children. Anti-androgens can suppress hirsutism but their long-term effects are unknown and they do have to be taken continuously. Only wedge excision of both ovaries permits a full resumption of ovarian function (normal ovulatory cycles) which has been found to be temporary by some workers and long-lasting by others. A major disadvantage of bilateral wedge excision is the formation of pelvic adhesions which may be responsible for iatrogenic sterility in 30% of women treated in this way.

On the assumption that numbers of androgen-producing cells could also be much reduced by unilateral oophorectomy (a shorter and easier operation than the bilateral wedge procedure), we have removed one ovary in ten patients with PCO.

In all ten patients adrenal disease was rulled out and the ovaries were clearly unequal in size. However, the unequal size was not always confirmed at laparotomy—in one case the ovaries were equal in size and in another the contralateral ovary turned out to be the larger one. The policy was to remove the larger ovary.

Postoperatively blood testosterone levels fell in all patients and became normal in eight. A regular ovulatory cycle developed immediately after surgery in all patients.

In five patients the indication for treatment was infertility and attempts to restore fertility with clomiphene had failed. Three of these patients, who were operated on in 1980, conceived within 6 months and have been delivered of healthy full-term babies. The remaining two patients were operated on very recently.

Echography has revealed that the remaining ovary has become normal in size and that the microcysts have disappeared. The hypertrichosis, present in all ten patients, has not got worse. There have been no new sites of hair growth and shaving and other hair removal techniques have usually been applied less frequently. At the request of one patient she was given anti-androgens. One patient who has had severe premenstrual tension and heavy periods after surgery regrets having decided to have the operation.

After a mean follow-up of 30 months there have been no relapses of PCO and all ten women still have regular ovulatory cycles. Blood testosterone levels have risen slightly in two patients.

This pilot study suggests that simple unilateral oophorectomy can probably replace bilateral wedge excisions from ovaries in patients with PCO.

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INTRACAVERNOUS INJECTION OF PAPAVERINE FOR ERECTILE FAILURE

SIR,—The mechanism for the filling of the cavernous bodies at the onset of erection is still in dispute.[1] Accidental intracavernous injection of papaverine during a surgical shunting procedure[2] produced a prolonged fully rigid erection of two hours' duration. This fact, combined with observation of improvement of erectile function reported by impotent patients after they had been subjected to artificial erection[3] for evaluation of erectile dysfunction,[4] led us to study the effect of intracavernous injection of papaverine.

The study was done after the thorough investigations (including nocturnal penile tumescence monitoring, pudendal arteriography, and bulbocavernous reflex latency measurements) that we recommend for evaluation of erectile dysfunction.[3,4] In this way we could classify cases as organic or non-organic impotence.

80 mg papaverine was injected into one of the cavernous bodies, after insertion into the other of a 21G plastic needle for continuous monitoring of intracavernous pressure (ICP). To study the condition of the arterial vessels, ultrasonic continuous measurement (Doppler method) and pulse plethysmography were used. Later, selective bilateral internal iliac arteriography was done. Our preliminary findings relate to fifteen organic cases and ten non-organic cases of impotence.

The immediate reaction was an increase in ICP, indicating volume changes and the development of pressure inside the cavernous bodies. The mean value of the ICP increase was much higher when the trial was done during general anaesthesia (mean ICP increase 70 mm Hg compared with 40 mm Hg without anaesthesia). This effect was related to increased arterial flow, as shown by Doppler studies, plethysmography, and arteriography. The peak effect, depending on the state of the arteries, was obtained after 2–15 min, and an effect lasted for from 10 to 120 min. There were no general or local complications.

Seven of the fifteen patients with an organic aetiology reported significantly improved erections in the days after the procedure, but none of the non-organic cases reported any changes in their erectile capability. All seven had arterial lesions in the distal part of the internal pudendal artery and/or in the cavernous arteries.

In the light of these results thirty impotent patients (including twelve with diabetes mellitus) who had Doppler and arteriographic evidence of arterial insufficiency were selected for conservative therapy. Intracavernous injection of papaverine (80 mg) was followed, after 15 min observation of the drug's effect, by infusion of 1% heparin in normal saline via an infusion pump, to obtain and maintain a rigid erection for a 15 min period. No anaesthesia was used.

The procedure was repeated 2 months later and then every third month or according to the clinical status. Of the fourteen patients (seven with diabetes) who had two or more artificial erections, four reported a return to a normal sexual life; nine described a significant improvement in penile rigidity; in one there was no effect and an arterial revascularisation procedure was done.

Few clinical studies have been done on the effects of drugs on penile erection.[5] No vasoactive drug has proved effective in controlled studies. Papaverine is a powerful smooth-muscle relaxant and has been used in laboratory studies of vasoactive drugs, as a control substance.[6] Two levels of action seem possible: inhibition of cyclic AMP phosphodiesterase[7] or an antinicotinic effect.[8] Artificial erections achieved with normal saline are associated with vasodilatation of branches of the pudendal arteries,[9] and we agree that there must be mechanical action at the level of the cavernous tissue.

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RELEASE OF HISTAMINE BY H_2-RECEPTOR ANTAGONISTS

SIR,—There has been a good deal of debate in *The Lancet* lately about cardiac effects of H_2-receptor antagonists. Earlier reports of cardiac dysfunction have largely concerned intravenous cimetidine.[1] We report here findings with both cimetidine and ranitidine given intravenously (i.v.).

The study followed a chance observation. We were investigating the release of histamine by plasma substitutes and seeking to prevent adverse effects. Before infusion of the plasma substitute

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TABLE I—INCREASE IN PLASMA HISTAMINE LEVELS (ng/ml): FIRST STUDY

Subject	After saline 0·2 ml/kg	After cimetidine 10 mg/kg	After cimetidine 5 mg/kg + chlorpheniramine 0·3 mg/kg
1	0	0	0
2	0	0	0
3	0	0	0·3
4	0	0	1·1
5	0·25	0·35	1·1
6	0·25	1·35	1·1
7	0·25	1·85	1·2
Total showing rise	*3/7*	*3/7*	*5/7*
Rise ≥1·0 ng/ml	*0/7*	*2/7*	*4/7*

TABLE II—INCREASE IN PLASMA HISTAMINE LEVELS (ng/ml): SECOND STUDY

Subject	After cimetidine 200 mg	After ranitidine 80 mg
1	0·2	0·1
2	0·9	0·1
3	0·2	0·1
4	0·2	0·7
5	0	0·1
6	0	0
7	0	0
8	0·2	0·2
9	0·9	0·1
Total showing rise	*6/9*	*7/9*
Rise ≥1·0 ng/ml	*0/9*	*0/9*

some subjects were given i.v. saline, some i.v. cimetidine, and some both cimetidine and chlorpheniramine. Blood was taken for plasma histamine assay by a fluorimetric method[2] which, because it does not depend on histamine methyltransferase, is valid in the presence of cimetidine and ranitidine. After cimetidine 10 mg/kg two subjects showed a rise in plasma histamine of more than 1 ng/ml (table I), giving levels which can produce cardiac arrhythmias in susceptible subjects.[3] When both cimetidine and chlorpheniramine were used four of the seven subjects showed a rise of at least 1 ng/ml. These results were worrying, but the cimetidine dosage was much greater than the conventional clinical dose and had been chosen on the basis of animal studies. We decided to investigate this further, using normal clinical doses of both ranitidine and cimetidine.

Ten subjects were given cimetidine 200 mg or ranitidine 80 mg i.v. over 30 s on consecutive days in a single-blind study. The order of the drugs was randomised. The study was confined to doctors who were fully informed of the nature and hazards of the investigation.

Satisfactory samples were obtained from nine doctors but in the tenth blood sampling was difficult and subsequent haemolysis made the proper preparation of plasma samples impossible. None of the nine subjects showed a plasma histamine rise of 1 ng/ml, nor was there any subjective evidence of histamine release.[4]

We conclude that there is a risk of a dangerous rise in plasma histamine if a high dose of cimetidine (and, possibly, other H_2-receptor blocking agents) is given by rapid i.v. injection. However, standard doses of cimetidine or ranitidine given by slow i.v. injection do not have this effect. The data sheets produced by Smith, Kline and French and Glaxo, respectively, emphasise the need for slow i.v. injection but casual observation suggests that the importance of this is not widely appreciated. Our studies suggest that injection over 30 s into a peripheral vein is safe. We have not information about the effects of H_2-receptor antagonists given into central venous lines, but it seems reasonable to suppose that this route may be particularly hazardous.

We have not identified the source of the histamine which can be released under these circumstances. However, human myocardial tissue contains approximately 1000 ng of histamine per g wet weight.[5] The release of only a small proportion of this histamine could give rise to severe cardiac arrhythmia[3] and the exact form of such cardiac effects seems likely to be unpredictable, especially if histamine receptors are already partly antagonised.

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LACK OF RESPONSE TO INTRAVENOUS CALCIUM IN SEVERE VERAPAMIL POISONING

SIR,—Verapamil is a slow calcium channel blocker which depresses sinus and atrioventricular node activity as well as producing a negative inotropic effect on the myocardium. Although this drug has been available for 20 years, only thirteen reports (seven in English[6-12]) of poisoning have been published, three of which include supporting analytical data.[6,7,12] We report here the most severe case of verapamil poisoning so far described.

A 39-year-old woman was admitted unconscious (grade 3 coma) after a presumed overdose. On admission she had an unrecordable blood pressure and bradycardia (48/min), but there were no focal neurological signs; ventilation was adequate after endotracheal intubation. An ECG showed alternating junctional and sinus rhythm with abnormal intraventricular conduction, first-degree heart block (PR 0·44 s) and negative P waves. There was circumstantial evidence of acute beta-adrenergic blocking drug overdosage so glucagon 10 mg, prenalterol 10 mg, and atropine 1·2 mg were given intravenously, but without improvement. Because of marked hypotension and anuria, infusions of dopamine (2·5 μg/kg/min), frusemide (2 mg/min), and dobutamine (increasing doses to 40 μg/kg/min) were started. 90 min after admission it was learned that the patient had ingested at least 1200 mg verapamil up to 18 h before admission, and this was confirmed analytically[13] (figure). Calcium gluconate (10%) 20 ml was given intravenously and within 30 min the intraventricular conduction abnormality became less marked. Thereafter calcium gluconate (10%) was infused to a total of 240 ml over 44 h, as an adjunct to other supportive measures. Despite the dobutamine infusion the blood pressure remained unrecordable and bradycardia persisted. An infusion of isoprenaline (5 mg over 30 min) was therefore started and continued at a rate of 2 μg/min. Within 15 min the pulse was 80/min and the blood pressure 90/60 mm Hg. Subsequently, on withdrawal of dobutamine, it was necessary to increase the dose of

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