the administration of intravenous sodium bicarbonate, his urinary output rose to 50 ml/hour. However, by the next day blood urea had risen to 38 mmol/l (229 mg/100 ml) and the urate level was unchanged. Urgent haemodialysis was performed, with biochemical improvement; in particular, postdialysis urate was 0.50 mmol/l (8.40 mg/100 ml). Following a single haemodialysis his diuresis continued over the next three days and his recovery was otherwise uneventful, with no residual renal impairment.

We agree that acute renal failure due to a nephrotoxic effect of alcohol is unlikely. In our case muscle damage was both apparent clinically and confirmed biochemically. However, the uric acid level was also grossly elevated. The mechanism of acute renal failure as a consequence of myoglobinuria is uncertain although it has been suggested that other factors, including shock and acidosis, are important.¹ It is well recognised that hyperuricaemia occurs following muscle damage.² Additionally, hyperuricaemia may lead to acute renal failure in the absence of muscle damage.³ Muscle damage may result from pressure necrosis following immobility during alcoholic stupor.⁴ We suggest that the resulting hyperuricaemia is a major aetiological factor in the development of acute renal failure in this situation.

In similar cases, priority should be given to the estimation of uric acid level and if it is grossly elevated then urgent alkalisation to increase uric acid solubility and dialysis to reduce uric acid load is indicated. In such circumstances haemodialysis is to be greatly preferred to peritoneal dialysis, as urate clearance is significantly greater.⁵

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² Warren DJ, Leitch AG, Leggett RJE. *Lancet* 1975; ii:385-7.

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Clearance of bacteriuria on discontinuing oral contraception

SIR,—Dr D A Evans and others (19 January, p 152) conclude from their study that "clearance of bacteriuria in women who take oral contraceptives is related to discontinuation of the pill." They do not state whether the women who discontinued remained sexually active—comparability of marital status between the two groups is not a sensitive indicator of this variable. The association between sexual activity and bacteriuria is well documented; those women who stopped taking the pill may have done so because they were no longer having intercourse. Without this information the authors' conclusion is invalid.

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SIR,—I find the short report on clearance of bacteriuria on discontinuing oral contraception (19 January, p 152) interesting but would like to know: (a) what forms of contraception were substituted for oral contraceptives; and (b)

whether there was any change in the frequency of sexual intercourse on stopping oral contraceptives. Both these factors could effect the occurrence of bacteriuria.

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SIR,—Dr D A Evans and others suggest (19 January, p 152) that clearance of bacteriuria in women who have been taking oral contraceptives is related to discontinuation of the medication. One cogent reason why women stop the contraceptive pill is that they stop having sexual intercourse, an activity known to be related to the incidence of urinary tract infection and bacteriuria.¹ The authors match their patients for marital status, but in 1980 I do not think that this accurately reflects sexual activity. Perhaps the reduction in bacteriuria is at least partly accounted for by a reduction in frequency of intercourse rather than discontinuation of the pill?

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¹ Kunin CM, McCormack RC. *N Engl J Med* 1968; 278:635-42.

*We sent copies of the first two letters to the authors, whose reply is printed below.—Ed, *BMJ*.

SIR,—The possibility raised by Dr Susan M Hall seems unlikely for two reasons. Contrary to her assumption that an association has been demonstrated between sexual activity and bacteriuria, we know of no adequate studies of the matter, a point that others have also emphasised.¹ Much of the suspicion that current sexual activity may be related to acquisition of urinary tract infection arises from anecdotes concerning symptomatic infections occurring soon after intercourse. Such observations are compatible with several other explanations, however, including acquisition of symptoms by women with pre-existing asymptomatic infection, the simple coincidence of infections with a frequent event, and over-reporting of striking clinical situations in a common ailment. Some support for an association may be inferred from a study² showing lower rates of bacteriuria for nuns than for women employed in the community. On the other hand, this same study and also population-based surveys³⁻⁵, including the one⁶ on which our report is based, have consistently shown that younger women in the most sexually active age groups⁶ have lower rates of bacteriuria than do older women.

Secondly, although we did not seek data on sexual activity in our study, some information may be gained from the reasons women gave for discontinuing oral contraceptives. Three of the women who stopped using them switched to another method (one an intrauterine contraceptive device, one the rhythm method, and the husband of the third had a vasectomy); one wished to become pregnant; one passed the menopause; and in two cases the reason for discontinuation was not known. Although these reasons give no quantitative estimate of sexual activity, they do not support the idea that an intent to abstain led to the discontinuation of oral contraception.

Dr Elizabeth M T Mayall raises another issue: that clearance of bacteriuria may have been related to the substitution of some new

method of contraception rather than to the actual discontinuation of oral contraception. For this mechanism to explain our findings would require that the risk of infection for women using some alternative means of contraception should be lower than that for women using no contraceptives. We know of no data supporting this idea. In addition, the variety of reasons given for stopping oral contraceptives make it unlikely that any single reason substantially modifies the association.

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Platelet-release reaction in myocardial infarction

SIR,—Dr S Heptinstall and others have demonstrated (12 January, p 80) that there is a significant difference between the platelet release reaction in patients who died within a year of myocardial infarction on the one hand and those who survived this period and control subjects on the other. This phenomenon was observed when heparin was used as anticoagulant but was masked by citrate. These observations are of considerable interest, especially if they are borne out in a larger series of patients.

We would like to suggest that the enhanced platelet release reaction in patients with poor prognosis may be related to decreased prostacyclin (PGI₂) activity. There is evidence that vessels damaged by atherosclerosis produce less PGI₂¹ and that PGI₂ may have a protective effect² (possibly including an antiarrhythmic action³) in the postinfarction period. This may account for the fact that more patients with poor prognosis had had previous infarcts than those with good prognosis.

There is evidence that heparin inhibits PGI₂ activity.⁴ Therefore a decreased PGI₂ activity could be significantly inhibited by heparin whereas higher activities in controls and patients with good prognosis would not. Furthermore, other workers have shown that in experimentally induced atherosclerosis in rabbits there is a distortion of the PGI₂: platelet thromboxane A₂ (TXA₂) ratio.⁵ More complicated mechanisms, therefore, possibly involving an increase in platelet TXA₂ activity, must also be considered.

Thus the inhibitory effect of heparin on PGI₂ may have some relevance to the observation of Dr Heptinstall and his colleagues. We would therefore like to know if the authors have investigated the effect on the release reaction of varying the concentration of heparin. Furthermore, there is also the question whether all the serotonin taken up by platelets in such an experiment is, in fact, incorporated into the same pool as endogenous serotonin.

Whatever the answers the ever present question remains: is what we observe in vitro a reflection of what really happens in vivo?

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² Ogletree ML, Lefer AM, Smith JB, Nicolaou KC. *Europ J Pharmacol* 1979;56:95-103.
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* * We sent a copy of this letter to the authors, whose reply is printed below.

SIR,—Drs Mikhailidis and Dandona ask whether the heparin used in our study may have interfered with the action of residual prostacyclin (PGI₂) on the platelet-release reaction. When we compared the extent of the release reaction in platelet-rich plasma (PRP) prepared from blood that contained 2, 10, or 100 units of heparin/ml (n=17), the mean amounts of ³H-serotonin released were 22% (SE of mean ± 3.7), 15% (± 3.8), and 4% (± 1.4) respectively. The differences in release at the three heparin levels were significant (P<0.01), so heparin reduces release rather than enhances it. Another factor that suggests to us that it is unlikely that a direct interaction between heparin and PGI₂ influenced the results that we obtained is the inherent instability of the latter. PGI₂ in aqueous solution loses its antiaggregatory activity within 20 minutes.¹ In our experiments the extent of release was determined some 90 minutes after blood had been withdrawn and it is unlikely that any PGI₂ remained in the plasma after this time.

It seemed possible to us that enhanced thromboxane A₂ production might account for the platelet hyperactivity observed in PRP from some individuals. Accordingly we compared the extent of release with the amount of malondialdehyde (a marker for thromboxane synthesis) that is produced when arachidonic acid is added to PRP.² We have, however, been unable to detect any relation between the two processes.

The final factual point raised by Drs Mikhailidis and Dandona relates to the validity of using ³H-serotonin as a marker of endogenous serotonin and hence of the extent of the release reaction. This relies, of course, on ³H-serotonin being taken up into the intracellular store that contains the endogenous serotonin. We have not verified this in our own studies but Costa and Murphy³ have shown that 0.1-1.0 $\mu\text{mol/l}$ (0.18-1.76 $\mu\text{g}/100\text{ ml}$) ³H-serotonin added to PRP is all taken up into the pool of endogenous serotonin. In our experiments we added 0.5 $\mu\text{mol/l}$ (0.88 $\mu\text{g}/100\text{ ml}$) ³H-serotonin to the platelet preparation.

Their final question is of crucial importance; we have repeatedly emphasised in other publications that there is no evidence which allows us to be sure that any of the aspects of platelet behaviour currently studied in vitro (aggregation, adhesion, release, β -thromboglobulin levels, platelet factor 4, and thromboxane and prostaglandin production) are of physiological or pathological significance. The relationships between in vitro and in vivo phenomena are not yet known, nor can we be

sure that agents which modify in vitro behaviour in a potentially favourable way will be antithrombotic in clinical test situations.

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- ¹ Moncada S, Gryglewski R, Bunting S, Vane JR. *Nature* 1976;263:663-5.
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³ Costa JL, Murphy DL. *Life Sci* 1976;18:1413-8.

Hirsutism and virilisation

SIR,—We were interested to read the review of hirsutism and virilisation (9 February, p 369). Drs Jean Ginsburg and Michael C White highlight the difficulties in the investigation and management of a complex clinical problem. However, we should like to make the following points.

The authors state that sclerocystic ovaries are a leading cause of hirsutism. While investigating a large group of female hirsute patients we have found that only 15% of them could possibly be considered to have sclerocystic ovaries by clinical and biochemical criteria and by ovarian ultrasonography. The diagnosis of sclerocystic ovaries—that is, ovaries with multiple cysts and subcapsular fibrosis—is essentially histopathological and would require ovarian biopsy, usually by laparoscopy, a procedure which is not without hazards. We agree, however, that ovarian dysfunction is the main abnormality in hirsute females. Ovarian dysfunction covers a range of diseases including sclerocystic ovaries. Since chronic anovulation is common in these conditions,¹ serum luteinising hormone concentrations and serial ovarian ultrasonography are helpful screening procedures in patients with clinical features suggestive of ovarian abnormality. We are concerned that the emphasis on sclerocystic ovaries might lead to excessive and unnecessary laparoscopic examinations, especially when confirmation of sclerocystic ovaries will not substantially affect the choice of treatment.

We would contest strongly that waxing should be avoided on the face. This treatment is an excellent method of removing hair from the face, even although it epilates the down. In our experience waxing does not result in scarring. To produce scarring dermal damage has to occur and it is difficult to see how this could arise with this method. Hot waxing is not a satisfactory method of hair removal from the abdomen and legs, as it is extremely time consuming. Hot wax cannot be applied to an area larger than 5 cm $\times$ 5 cm at any one time, as the wax hardens too quickly if applied to larger areas and then becomes impossible to pull off rapidly. Obviously on larger areas such as the limbs waxing would take a considerable time. There are effective "cold" wax strips which are useful for the abdomen and limbs but they are expensive and can only be used once, while the hot wax can be reused. Electrolysis can cause very unsightly scarring if performed by an inexperienced operator.

We would suggest that care is taken in the selection of a progestogen for combination with ethinyloestradiol and prednisolone. n-norgestrel and norethisterone acetate, two of the most commonly prescribed progestogens, can significantly lower sex-hormone-binding

globulin and hence increase the concentrations of unbound testosterone.² The combination of levonorgestrel (n-norgestrel) with 30 μg of ethinyloestradiol or 1 mg norethisterone acetate with 50 μg of ethinyloestradiol would appear to be appropriate choices.

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- ¹ Yen SSC. *Clin Endocrinol* 1980;2:177-208.
² El Makhzangy MN, Wynn V, Lawrence DM. *Clin Endocrinol* 1979;10:39-45.

Possible cancer hazard associated with 5-methoxypsoralen in suntan preparation

SIR,—I would like to support Professor M J Ashwood-Smith's letter (3 November, p 1144) on the potential hazards of including psoralens in suntan preparations.

All psoralens that have a photosensitising effect enhance the DNA damage caused by ultraviolet light, as admitted by Dr P Forlot in his reply (1 March, p 648). This increased "injury" is perhaps acceptable in psoriatic patients, who may by virtue of their disease have an increased resistance to mutagenesis, but is not so in normal fair-skinned individuals, who have a limited ability to tan and rely heavily on the protective qualities of suntan preparations to allow them to disport themselves in the sun at all.

It seems completely unjustified with our present knowledge to expose this highly susceptible group to a substance that has been clearly shown to be mutagenic. If photosensitisers must continue to be added to suntan preparations at least let the containers be clearly marked as such so that the choice rests with an informed public.

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SIR,—The letter of Dr P Forlot (1 March, p 648) concerning the use of 5-methoxypsoralen in suntan preparations requires some comments.

So far as we know, the 5-methoxypsoralen in suntan preparations is used in the form of natural oil of bergamot and not as a pure chemical, according to the actual EEC regulations. From the point of view of the chemical itself, the mutagenic effects of 8-methoxypsoralen and 5-methoxypsoralen have been studied in vitro by Pool *et al*¹ and Hoffnung *et al* (unpublished observations). 8-Methoxypsoralen and to a lesser extent 5-methoxypsoralen have yielded a weakly positive reaction in the Ames test, this reaction being comparable with that of caffeine.

Our statistics for a single PUVA therapy centre (where over a four-year period 1359 patients have been treated with 8-methoxypsoralen²), the results of the French national survey carried out over this same period for 4000 patients, and the European statistical study of 3000 patients (Christophers, personal communication) have all yielded results different from those of Stern³ in that no case