in the absence of any clinical or biochemical evidence of liver damage, as shown by the following case reports.

The first patient was a 21-year-old man who was admitted three days after allegedly taking 15 g of paracetamol. Three days after admission the plasma creatinine peaked at 256 μmol/l (2·89 mg/100 ml) and the creatinine clearance was 38 ml/min. The second was a woman of 22 years who was admitted 12 hours after taking paracetamol and Veganin (containing aspirin 250 mg, paracetamol 250 mg, and codeine phosphate 9·58 mg per tablet). The plasma concentrations of paracetamol and salicylate were 50 and 125 μg/ml respectively and treatment with *N*-acetylcysteine was begun. The plasma creatinine concentration was 85 μmol/l (0·96 mg/100 ml) on admission but rose to 390 μmol/l (4·41 mg/100 ml) on the sixth day while the creatinine clearance fell to 10 ml/min. The third patient, a 23-year-old man, was admitted 11 hours after taking paracetamol in overdosage with a plasma concentration of 86 μg/ml. At the time D-penicillamine was being investigated as a possible antidote for paracetamol poisoning and he received 5 g intravenously over 20 hours. The plasma creatinine concentration rose to 450 μmol/l (5·0 mg/100 ml) on the fifth day. Serial liver function tests (including prothrombin time) remained normal throughout in all three cases, but all had proteinuria with red cells and tubular casts in the urine. Renal function was normal in all at follow-up one month later.

In overdosage paracetamol causes renal tubular necrosis in the same way that it damages the liver—that is, through the covalent binding of a highly reactive metabolite which is normally trapped by conjugation with reduced glutathione.[3] Thus sulphydryl compounds such as *N*-acetylcysteine prevent renal as well as hepatic damage after paracetamol overdosage if given within 10 hours.[4] The possibility of renal failure should always be kept in mind in patients who have not received adequate treatment for paracetamol poisoning. In our experience this complication is invariably heralded by back pain with proteinuria and haematuria within 36-48 hours of ingestion of the paracetamol.

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Acetazolamide and symptomatic metabolic acidosis in mild renal failure

SIR,—Drs D N Maisey and R D Brown (5 December, p 1527) drew attention to acidosis caused by the acute introduction of acetazolamide in patients with renal impairment. We here report the occurrence of clinically significant hyperchloraemic acidosis in a diabetic woman on long-term treatment with the drug.

A 46-year-old insulin-dependent diabetic with proteinuria (1·6 g/day), but with normal urea and creatinine, had been treated for neovascular glaucoma with acetazolamide 500 mg twice daily for two years. She developed hyperglycaemic ketoacidosis as a result of septicaemic illness, having previously been well controlled on twice-daily isophane insulin. Following treatment with intravenous saline, insulin, and antibiotics, the ketoacidosis and hyperglycaemia resolved, but she remained clinically and biochemically severely acidotic. After three days the acetazolamide was withdrawn and she made a rapid recovery. When she was rechallenged with acetazolamide (500 mg twice daily) for five days asymptomatic acidosis recurred (table), and remained until the drug was stopped.

Although prolonged hyperchloraemic acidosis may follow diabetic ketoacidosis under other circumstances,[1] we believe that in this case it was caused by acetazolamide. This draws attention to the risk of acidosis in those who are on long-term treatment with the drug, even if they have a normal serum creatinine. As patients with diabetes mellitus are susceptible both to mild renal impairment and to metabolic acidosis, this risk should be borne in mind when acetazolamide is prescribed.

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Hyperchloraemic acidosis in diabetic woman treated with acetazolamide

(The ketoacidotic illness started on 2 November 1981; acetazolamide was discontinued on 5 November and reintroduced on 15 November.)

	Date	Cl^- (mmol/l)	pH	P_{CO_2} (kPa)	HCO_3^- (mmol/l)	Base excess (mmol/l)
Before ketoacidosis	16 Sept	116	—	—	16·0	—
After ketoacidosis:						
On acetazolamide	5 Nov	113	7·19	4·40	11·3	−13·7
Off acetazolamide	6 Nov	100	7·40	5·09	23·3	0·0
Acetazolamide challenge	20 Nov	106	7·29	4·23	15·1	−8·0

Conversion: SI to traditional units—Chloride, bicarbonate, and base excess: 1 mmol/l = 1 mEq/l. P_{CO_2}: 1kPa ≈ 7·5 mm Hg.

Failure with the new triphasic oral contraceptive Logynon

SIR,—The report by Mr R A Fay (2 January, p 17) about the new triphasic oral contraceptive Logynon is disturbing. I wish to draw attention to another aspect of this preparation—that of possible failure in the first course and the lack of instructions to the patient to use additional contraceptive precautions when starting Logynon.

An 18-year-old patient of mine, who had not previously used a contraceptive, started Logynon on the first day of menstruation, as recommended. This period lasted five days and was entirely normal. She completed a 21-day course without omitting any tablets and without having any gastrointestinal disturbance. This course was followed by amenorrhoea. When seen 10 days later she was found to have a normal-sized uterus and an equivocal result in the Gravindex pregnancy test. After a further 10 days she noted symptoms of pregnancy and was found to have uterine enlargement and was definitely positive in the Gravindex test. It seems most probable that this girl became pregnant during the first course of Logynon. I do not doubt that she took the course conscientiously.

I am concerned because when this triphasic preparation was first launched I understood that additional contraceptive precautions were not necessary when Logynon was started, if the course was started on the first day of the period. This would be consistent with the findings of suppression of mid-cycle gonadotrophins and oestradiol and late-cycle progesterone from the first treatment cycle. The instruction leaflet for patients does not advocate additional precautions unless the woman is changing from another oral contraceptive and starting on the fifth day of menstruation.

With monophasic contraceptives marketed by Schering, the need for additional precautions in the first 14 days after starting the pill is clearly stated in the instruction leaflet. If other similar instances of pill failure have been noted when the woman has been starting Logynon, perhaps the instruction leaflet should recommend additional contraceptive measures for the first two to three weeks.

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**We sent a copy of this letter to Dr Bye, of Schering Chemicals Limited, whose reply is included in the letter below.—ED, *BMJ*.

SIR,—The case report by Mr R A Fay (2 January, p 17) of a pregnancy in a user of Logynon is unremarkable, coming as it does 20 months after Schering's introduction of that highly successful oral contraceptive.

It is, of course, impossible to work out the "theoretical" efficacy of an oral contraceptive, since the investigator can never be sure what errors of administration have occurred, this being in the hands of the users. Moreover, even if in trials involving thousands of cycles administration could be independently verified, the limits of confidence for such rare events as pregnancies in trials of combined oral contraceptives are such that "theoretical" efficacy could never be accurately quantified.

What is of practical importance, however, is use effectiveness. Past experience shows that this varies widely from series to series because of the overwhelming effect of errors in the administration. Nevertheless, after a number of years of experience of the use of combined oral contraceptives by millions of women in different countries, a consensus of opinion was formed that the failure rate was of the order of 0·1 per 100 women-years. Clinical trials of Logynon, conducted before its introduction into Britain, gave no reason to assume that its efficacy was not of the same order.

Now, since the introduction of Logynon, over 3 million packs have been sold and, with sales of the same formulation by Wyeth, total sales since the introduction of the formulation have exceeded 5 million cycles. Even if we allow for the fact that some of these packs will not yet have been used, with a failure rate of 0·1 per 100 women-years well over 400 pregnancies would by now have been expected. It would be absurd to suggest that the case reported by Mr Fay and the seven reported to the Committee on the Safety of Medicines give any indication of the true total, but equally absurd to conclude that they are any cause for concern.

The same general observations apply to the pregnancy that Dr Graham reports. The probability of conception during one cycle of unprotected coitus has been estimated at about