affinity chromatography from the plasma of most patients with abruptio placentae shows evidence of both thrombin and plasmin activity. This has been demonstrated by an increase in *N*-terminal glycine (presumptive evidence of thrombin action) and, on SDS-polyacrylamide gels, of γ - γ dimers, D-D dimers (both thrombin and plasmin with factor XIII), together with α - and β -chain degradation (plasmin action). While it is possible that these breakdown products could be due to other (as yet unidentified) enzymes with properties similar to thrombin and plasmin, we must for the moment accept that abruptio placentae is probably associated with both thrombin and plasmin activity and the tendency to thrombosis may, in theory at least, be potentiated by antifibrinolytic therapy.

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SIR,—It is difficult to endorse the treatment of abruptio placentae with tranexamic acid as recommended by Dr B Åstedt and Professor I M Nilsson (25 March, p 756; 13 May, p 1277). We have shown that there is an inhibition of the fibrinolytic system as measured by the plasma euglobulin lysis time in 18 patients with abruptio placentae.¹ A fibrinolytic inhibitor would appear to be contraindicated in these patients. Also there has been a suggestion in the literature that some patients with potential for abruptio placentae, such as patients with renal disease or previous infarcted placenta, could benefit from heparin therapy.²

It is exceedingly rare to have a minor degree of bleeding which could serve as a warning sign in abruptio placentae. Once the abruptio placentae is significant enough to produce clinical symptoms termination of the pregnancy usually occurs before long-term treatment could alter its course, as early delivery is mandatory for maternal wellbeing. We had an opportunity to monitor carefully the third pregnancy of a patient with recurrent abruptio placentae and no previous fetal survival. When abruptio placentae occurred at 35 weeks, with the patient in hospital for precautionary observation from week 26 of pregnancy, it was sudden, without any bleeding or other clinical symptoms suggestive of impending abruption. This is typical of the vast majority of patients in whom there is a severe abruptio placentae with the potential for serious, clinically evident, defibrination. In most of these cases intrauterine fetal death occurs before active management can be instituted. Once abruptio placentae was recognised haematological management of these patients consisted of substitution therapy—that is, fresh frozen plasma and packed cells to replace the coagulation factors, plasma volume, and oxygen-carrying capacity without resorting to heparin or any anti-fibrinolytic agent. The fibrinogen concentration returned to pre-existing or normal

levels within 24 h and fibrin-related antigen values became normal within 48 h.

With modern attitudes toward perinatal problems and improved socioeconomic conditions it appears that serious abruptio placentae, threatening both mother and fetus, is less frequently encountered. In the past two years severe abruptio placentae has been encountered in only five women out of 6550 deliveries in this hospital in New York City despite its high-risk indigent population.

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Cardiac arrhythmias due to chloral hydrate poisoning

SIR,—Two cases of cardiac arrhythmia after an overdose of chloral hydrate were recently reported by Dr A J Marshall (15 October 1977, p 994) and it was noted that this adverse reaction was otherwise poorly documented. However, cardiac arrhythmias have been reported previously in several cases of chloral hydrate overdose¹⁻⁷ and we too have been concerned that this problem may be more frequent than is generally appreciated.

Between January 1975 and April 1978 the National Poisons Information Service received case summaries on 76 patients who had taken overdoses of chloral hydrate. Forty-seven of these were severely poisoned, being in grade III-IV coma; eight of the 47 were children aged less than 5 years and 39 adults aged over 18 years (average age 37 years). Cardiac arrhythmias occurred in 12 of the adults. Five suffered cardiac arrest but were successfully resuscitated, although one died several weeks later as a result of brain damage thought to be due to cerebral anoxia at the time of the arrest. The other seven patients were reported to have ventricular tachycardia or multifocal ectopic beats but did not develop severe cardiac dysfunction. Four of these 12 patients had taken other drugs (amitriptyline, glutethimide, salicylate, paracetamol, and flurazepam). The exact amounts of these drugs taken and plasma drug levels attained are not known, but from the history given chloral hydrate was considered to be the dominant drug and three of the five cardiac arrests occurred in patients who took only that drug.

Blood levels of trichloroethanol, the main metabolite of chloral hydrate, were measured in 12 cases within the first 24 h after ingestion. Five patients who had cardiac arrhythmias had blood levels of 66.5-210 mg/l and seven patients without cardiac symptoms had blood levels of up to 180 mg/l of trichloroethanol. We have insufficient information to form any opinion on the relationship between plasma levels and cardiac effects.

At least one case was reported to us in which the arrhythmia was controlled by a lignocaine infusion, and we would recommend treatment with antiarrhythmic drugs so long as there is no evidence to suggest otherwise. There is evidence that the active metabolites of chloral hydrate are adsorbed to charcoal,⁸ and in prolonged coma (>48 h) and deteriora-

tion of clinical condition we therefore recommend haemoperfusion or, if not available, haemodialysis.

In our experience extrasystoles in chloral hydrate poisoning seem to be quite common and should be expected in around 25% of cases.

We gratefully acknowledge the help of Mr R J Flanagan and the Poisons Unit Laboratory staff who estimated the drug levels.

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Rubella vaccination and pregnancy

SIR,—Dr Fiona Strang and her colleagues (29 April, p 1144) have noted a very important aspect of rubella vaccination of postpubertal women—namely, that rubella vaccine should be administered only to those women known to be susceptible.¹ It is clear that rubella vaccine virus can cross the placenta and infect the fetus during the early stages of development.² However, the frequency with which vaccine virus infects the fetus is difficult to estimate. Modlin *et al*³ reported that 21% of women known to be susceptible at the time of vaccination had culture-positive abortion specimens. This figure is similar to the 25% reported by Vaheri *et al*.³

This division also has information on the offspring born to 65 women susceptible to rubella (that is, haemagglutination inhibition antibodies to rubella at titres of <1/10) who either were inadvertently vaccinated while in the very early stages of pregnancy or conceived within the three-month period following vaccination, a period during which the Advisory Committee on Immunisation Practices of the United States Public Health Service recommends vaccinees to avoid pregnancy.⁴ All 65 infants were born without apparent abnormalities. However, two have laboratory evidence of fetal infection: one with a rubella-specific IgM antibody titre of >1/4 and one with a persistently elevated IgG level. These two children, aged 18 months and 22 months respectively, continue to have no apparent clinical abnormalities. A detailed report is in preparation.

Extrapolating from the binomial distribution based on these 65 observations, although there have been no observed malformations, the maximum risk of a congenital malformation occurring in these circumstances is 5.5% (95% confidence limits). This is similar to the risk of any pregnancy resulting in a congenitally malformed infant simply by chance.⁴ Thus, while the likelihood of recovering the vaccine virus from aborted material is substantial, the risk of congenital malformations occurring if the pregnancy is allowed to go to term appears to be far less.

The maximum risk of congenital malformations has decreased as the reported number of cases of rubella vaccination complicating a pregnancy has increased.² This division continues to collect such data and encourages the reporting of all such cases so that we may more exactly characterise the risks involved.

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¹ *Morbidity and Mortality Weekly Reports*, 1977, 26, 385.

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³ Vaheri, A, *et al*, *New England Journal of Medicine*, 1976, 296, 1071.

⁴ McIntosh, R, *et al*, *Pediatrics*, 1954, 14, 505.

Iodine and acetone-containing plastic spray dressings

SIR,—I read with interest the letter from Dr J Morgan-Hughes and Mr R A Bray (26 August, p 639) on the hazard of using Op-Site in conjunction with tincture of iodine and Slek waterproof plaster and would like to suggest a simple solution.

The back of the patient is prepared with a solution of 0.5% chlorhexidine in 70% spirit, which is allowed to dry before tincture of iodine is applied to a small area immediately over the proposed puncture site. The epidural cannula is then inserted in the normal manner and the puncture site sprayed with Op-Site. A folded gauze swab is inserted under the catheter and the whole area which has been painted with tincture of iodine covered by another 7.5 × 7.5 cm (3" × 3") gauze swab. Slek plaster may then be applied.

This technique has two advantages: (1) If there is an unknown allergy to iodine only a very small area of skin is affected rather than the whole area of back prepared. (2) The swabs prevent contact between the skin prepared with tincture of iodine and the Op-Site and Slek plaster, thus preventing all three substances coming into contact together, which apparently is the most precipitating cause of the blistering. Using this technique, I have never seen blistering of the skin occur in patients undergoing epidural analgesia, even when the catheter has been in situ for up to five days.

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Neonatal chlamydia conjunctivitis

SIR,—Dr Pamela Davies (2 September, p 676), in her review of neonatal infections, does not mention recent evidence that neonatal chlamydial conjunctivitis is very often not eradicated by topical chlortetracycline alone, perhaps because the organism is usually also present in the nasopharynx.^{1,2} Chlamydial infection acquired at birth may also cause significant respiratory symptoms in infants more commonly than previously realised^{3,4} and it therefore seems reasonable to give systemic treatment in the form of oral erythromycin for two weeks in addition to chlortetracycline eye ointment.

Sulphacetamide eye drops may not be the best routine treatment for "sticky eyes" which are not thought to be chlamydial or gonococcal. In the early stages of chlamydia

conjunctivitis the infection may not appear different from the ordinary "sticky eye" due to other organisms. The use of sulphacetamide or chloramphenicol eye drops may produce apparent resolution of the infection, which will recur later on stopping antibiotics and may persist for weeks or months unless proper treatment is given. It is therefore important to make a positive diagnosis of chlamydial infection before giving antibiotics which may be only suppressive rather than curative. Neomycin does not suppress chlamydia and we therefore suggest that this is the logical initial antibacterial treatment of "sticky eyes" in neonates. If the conjunctivitis persists despite neomycin ointment chlamydial infection is a strong possibility and swabs should be taken for chlamydial culture.

Finally, when a diagnosis of neonatal chlamydial conjunctivitis is made the parents should also be investigated, and treated if they are harbouring the organism.

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¹ Beem, M O, and Saxon, E M, *New England Journal of Medicine*, 1977, 296, 306.

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Penicillamine and previous treatment with gold

SIR,—Drs M Webley and E N Coomes (8 July, p 91) recently raised an important point for clinicians treating patients with rheumatoid arthritis (RA) when they presented data which suggested that adverse reactions to penicillamine are more common in patients who have previously been treated with gold than in those who have not. This prompted a review of 117 patients with classical or definite RA treated with penicillamine, the minimum follow-up being two years. There was no significant difference in the incidence of penicillamine adverse effects between those who had previously received gold (25/59) and those who had not (21/58). However, a different picture emerged when the patients treated with gold were subdivided into those in whom gold had been stopped because it was ineffective and those in whom it had been abandoned because of mouth ulcers, dermatitis, or proteinuria. Adverse effects due to penicillamine (thrombocytopenia, pemphigus, or proteinuria) developed in 10 of the 36 patients who had had no toxic reaction to gold and in 15 of the 23 patients who had had such a reaction. This difference is significant (0.02 > P > 0.01). In this analysis other adverse effects attributed to penicillamine—notably dyspepsia, abnormalities of taste, "feeling awful," and rashes occurring in the early weeks of treatment—were discounted as they are not of serious import, lack specificity, and can often be overcome by manipulations of dose.

This analysis clearly shows that patients who have to stop gold treatment because of an adverse effect are significantly more prone to develop a major adverse reaction to penicillamine. The implication of this is that penicillamine should be used with great caution, if at all, in patients known to have reacted adversely

to earlier treatment with gold. Furthermore, since a clinician contemplating the use of penicillamine may be unaware of a gold reaction because records are incomplete or unavailable or the patient's memory unreliable, it would be prudent to follow the counsel of Webley and Coomes, who wrote, "It would be sensible to take extra care in the supervision of patients starting on penicillamine if they have had gold treatment."

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Maprotiline hydrochloride and grand-mal seizures

SIR,—The case reports of Drs G A A Shepherd and F Kerr (10 June, p 1523) document once more the occurrence of grand-mal seizures during treatment with maprotiline hydrochloride (Ludomil). Recently a similar case has been seen at this hospital.

A 20-year-old nurse had been started on maprotiline 75 mg at night by her general practitioner because of depression and poor sleep pattern. Two weeks later the dosage was increased to 300 mg at night. She developed a tremor of her hands and unsteadiness on her feet and seven days after starting the higher dosage sustained two grand-mal seizures. There was no past or family history of epilepsy and her only other medication was the contraceptive pill (Ovranette). Physical examination was normal and an electroencephalogram nearly four months later showed only a mild theta dysrhythmia with no paroxysmal features.

Grand-mal seizures after overdosage of maprotiline have been well documented.^{1,2} The increasing number of reports of convulsions occurring during treatment with recommended doses is disturbing. The incidence of this side effect among patients taking maprotiline is not yet known and is an important deficiency in our knowledge of this drug.

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¹ Meek, D, *et al*, *British Medical Journal*, 1975, 2, 275.

² Park, J, and Proudfoot, A T, *British Medical Journal*, 1977, 1, 1573.

HLA B27 and risk of ankylosing spondylitis

SIR,—Your excellent editorial on this subject (2 September, p 650) contains a sentence which might be unfortunate for many with ankylosing spondylitis if it were interpreted uncritically—namely, "Boys known to be B27-positive might select physically undemanding jobs that they would be able to keep if they developed ankylosing spondylitis."

Most physically undemanding jobs are sedentary jobs and involve sitting at a desk or in a car and are probably the worst sort of job that a patient with ankylosing spondylitis might get, particularly if he has to work overtime. Spondylitis as a group are stout-hearted individuals who successfully manage physically demanding work and appreciate the ability to move around and exercise their backs to avoid stiffening and the loss of the upright posture to which they are liable. The proper approach surely is to let B27-positive